PHARMACEUTICAL SALTS OF VALDECOXIB

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60/PRTS

PHARMACEUTICAL COMPOSITIONS WITH IMPROVED DISSOLUTION

RELATED APPLICATIONS

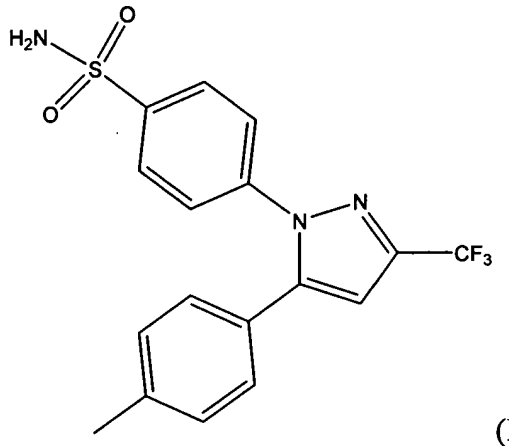
This application claims priority from U.S. Provisional Patent Application No. 60/412,459 filed on September 20, 2002; U.S. Provisional Application No. 60/426,275, filed on November 14, 2002; U.S. Provisional Application No. 60/427,086 filed on November 15, 2002; U.S. Provisional Application No. 60/429,515 filed on November 26, 2002; U.S. Provisional Application No. 60/437,516 filed on December 30, 2002; and U.S. Provisional Application No. 60/456,027 filed on March 18, 2003 which are hereby incorporated by reference for all purposes.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions and methods for preparing same.

BACKGROUND OF THE INVENTION

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) is a substituted pyrazolylbenzenesulfonamide represented by the structure (I):

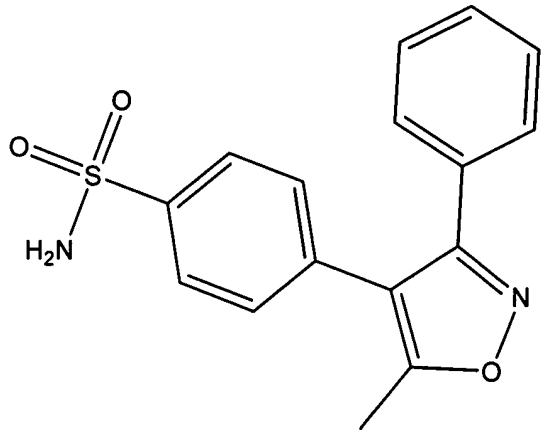


(I)

Celecoxib belongs to the general class of non-steroidal anti-inflammatory drugs (NSAIDs). Unlike traditional NSAIDs, celecoxib is a selective inhibitor of cyclooxygenase II (COX-2) that causes fewer side effects when administered to a subject.

The synthesis and use of celecoxib are further described in U.S. Pat. Nos. 5,466,823, 5,510,496, 5,563,165, 5,753,688, 5,760,068, 5,972,986, 6,156,781, and 6,579,895, the contents of which are incorporated by reference in their entirety. Orally deliverable liquid formulations of celecoxib are discussed in U.S. Patent Application Publication No. 2002/0107250 in the name of Hariharan, et al., the contents of which are incorporated herein by reference in their entirety.

Valdecoxib, 4-(5-methyl-3-phenyl-4-isoxazolyl)benzene sulfonamide, is a substituted isoxazolyl benzenesulfonamide represented by the structural formula (II):



(II).

Valdecoxib also belongs to the general class of non-steroidal anti-inflammatory drugs (NSAIDs) and is another selective inhibitor of cyclooxygenase II (COX-2). The synthesis and use of valdecoxib are further described in U.S. Patent Nos. 5,633,272, 5,932,598, 5,985,902, 6,323,226, 6,384,034, 6,403,640 and 6,413,965, and U.S. Publication Nos. 2002/0013357, 2002/0015735, 2002/0034542, 2002/0071857, 2002/0107250 and 2002/0119193, the contents of which are incorporated herein by reference in their entirety.

Other COX-2 inhibitory drugs are related to celecoxib and valdecoxib, which form part of a larger group of drugs, all of which are benzene sulfonamides. These include: deracoxib, which is 4-[3-fluoro-4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-1-yl]benzene sulfonamide; rofecoxib, which is 3-phenyl-4-[-(methylsulfonyl)phenyl]-5H-furan-2-one; and etoricoxib, which is 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine. These drugs are described in further detail in WO 01/78724 and WO 02/102376.

In its commercially available form, trademarked as CELEBREX, celecoxib is a neutral molecule that is essentially insoluble in water. Celecoxib typically exists as needle-like crystals, which tend to aggregate into a mass. Aggregation occurs even when celecoxib is mixed with other substances, such that a non-uniform mixture is obtained. These properties are shared by other pyrazolylbenzenesulfonamides and present significant problems in preparing pharmaceutical formulations of the drugs, particularly oral formulations.

Valdecoxib, commercially available as BEXTRA™, is also a neutral molecule that is essentially insoluble in water. Several strategies have been employed to increase the water solubility of valdecoxib, but these involve additional synthetic steps and the conversion of valdecoxib into a prodrug (e.g., through acylation). An alternative strategy is to dissolve netural valdecoxib in an organic solvent (e.g., a glycol) and administer the valdecoxib-containing solution.

It would be advantageous to provide new forms of drugs that have low aqueous dissolution which have improved properties, in particular as oral formulations. Moreover, even where an active pharmaceutical ingredient (API) of low aqueous solubility is provided in a form which has improved aqueous solubility, there still exists a problem when dissolution of the drug is required, for example after having been taken as an oral formulation where the drug becomes diluted in the alimentary canal. (The terms "API" and "pharmaceutical" are used herein interchangeably.) In this situation, APIs having low aqueous solubility tend to come out of solution. When this happens, for example by a process of crystallization or precipitation, the bioavailability of the API is significantly decreased. It would therefore be desirable to improve the properties of formulations containing such APIs so as to increase the bioavailability of the API in an orally-administered form, thereby providing a more rapid onset to therapeutic effect.

SUMMARY OF THE INVENTION

It has now been found that stable, crystalline salts and co-crystals of celecoxib and valdecoxib can be synthesized. The celecoxib and valdecoxib compositions of the present invention have a greater solubility, dissolution, total bioavailability (area under the curve or AUC), lower T_{max}, the time to reach peak blood serum levels, and higher $C_{max,}$, the

maximum blood serum concentration, than their neutral counterparts. The compositions of the present invention also include compounds that are less hygroscopic and more stable. The salts of the present invention when in crystalline form convert to either an amorphous free form upon neutralization of the salt, which subsequently converts to a neutral metastable crystalline form or directly to a neutral metastable crystalline form. These amorphous and metastable crystalline forms are more readily available forms of the API than are presently-marketed neutral celecoxib and valdecoxib. Neutral crystalline celecoxib, presently-marketed as CELEBREX™, and neutral crystalline valdecoxib, presently-marketed as BEXTRA™, are designated as "neutral" to distinguish from the ionized salt forms of the APIs. In addition, acidification or neutralization of a solution of either pharmaceutical salt *in situ* yields amorphous API, which subsequently converts to a metastable crystalline form or directly to a neutral metastable crystalline form of neutral API before finally converting into stable, neutral molecules.

An aspect of the present invention relates to methods of increasing dissolution, solubility, and or the time an API (either alone or as part of a pharmaceutical composition), can be maintained, upon dissolution, as a supersaturated solution, before precipitating out of solution. The increase in dissolution (or concentration as a function of time) results in, and thus can be represented by an increase in bioavailability, AUC, reduced time to T_{max} or increased C_{max}. The methods comprise the steps of making a salt or co-crystal from an API (e.g. free acid) and combining the salt or co-crystal with a precipitation retardant and optionally, a precipitation retardant enhancer (referred to as enhancer hereafter). The term "precipitation" refers to either a crystalline or amorphous solid form separating or "coming out of" the solution. The salt may be amorphous or crystalline, but is preferably crystalline. Normally the salt or co-crystal form used is in a crystalline form that dissolves and then **re**crystallizes and precipitates out of solution, which is why the term "crystallization" retardant may be used in place of "precipitation" for greater specificity. The term "crystallization" retardant can also be used to specify a salt or co-crystal that was in amorphous form prior to dissolution, and precipitates out of solution in crystalline form after dissolution. Crystalline salts are superior to amorphous salts as the initial compound, with an amorphous salt being superior to a neutral amorphous or crystalline form. Free acid forms are not preferred initial compounds unless first solubilized in a solubilizer

resulting in a liquid formulation comprising a precipitation retardant and optional enhancer. The precipitation retardant is often a surfactant, preferably a surfactant with an ether functional group, preferably a repeating ether group, e.g., an ether group repeated at least two or three times wherein the oxygen atoms are separated by 2 carbon atoms. Further preferred surfactants have an interfacial tension of less than 10 dynes per centimeter when measured at a concentration of 0.1 %w/w in water at 25 degrees C and/or the surface tension of the precipitation retardant (e.g., poloxamers) is less than 42 dynes/cm when measured as a concentration of 0.1 %w/w in water at 25 degrees C. The combination of salt or co-crystal, precipitation retardant and an optional enhancer (or precipitation retardant, an optional enhancer and some other form) preferably prevents or delays precipitation of a supersaturated solution by about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, or 60 minutes or greater than 1 hour in an aqueous solution, preferably water or gastric fluid conditions such as the gastric fluids of an average human stomach fasted for 12 hours or simulated gastric fluid (SGF). Preferably, the solution remains supersaturated for more than 15, 20, or 30 minutes to allow the composition to move out of the stomach and into an environment with a higher pH. The SGF may be diluted by 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold to represent water intake. For example, the SGF may be diluted 5 fold to represent a patient drinking a glass of water at the time a composition of the present invention is taken orally. The degree of increase in solubility, dissolution, and/or supersaturation may be specified, such as by 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100%, or by 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold greater than thefree acid in the same solution. The increase in dissolution may be further specified by the time the composition remains supersaturated.

The enhancer preferably comprises a cellulose ester such as hydroxypropylcellulose (HPC) or hydroxypropylmethylcellulose (HPMC). Thus according to the methods of the present invention, supersaturated concentrations upon which a drug may be maintained upon dissolution and/or the degree of dissolution of a drug in gastric fluid conditions (e.g., SGF) is enhanced.

Normally, the enhancer does not improve or only minimally improves (less than/equal to 10%) the length of time the API can remain supersaturated without the

additional presence of the precipitation retardant. The methods of the present invention are used to make a pharmaceutical drug formulation with greater solubility, dissolution, and bioavailability, AUC, reduced time to T_{max}, the time to reach peak blood serum levels, and higher $C_{max,}$, the maximum blood serum concentration, when compared to the neutral form or salt alone. AUC is the area under the plot of plasma concentration of drug (not logarithm of the concentration) against time after drug administration. The area is conveniently determined by the "trapezoidal rule": the data points are connected by straight line segments, perpendiculars are erected from the abscissa to each data point, and the sum of the areas of the triangles and trapezoids so constructed is computed. When the last measured concentration (C_n, at time t_n) is not zero, the AUC from t_n to infinite time is estimated by C_n/k_{el}.

The AUC is of particular use in estimating bioavailability of drugs, and in estimating total clearance of drugs (Cl_T). Following single intravenous doses, AUC = D/Cl_T, where D is the dose, for single compartment systems obeying first-order elimination kinetics; alternatively, AUC = C_0/k_{el}, where k_{el} is the drug elimination rate constant. With routes other than the intravenous, AUC = $F \cdot D/Cl_T$, where F is the absolute bioavailability of the drug.

The invention further relates to wherein a precipitation retardant and an optional enhancer is combined with a pharmaceutical that is already in a salt or co-crystal form. The invention further relates to wherein a precipitation retardant and an optional enhancer is combined with a pharmaceutical that is a solvate, desolvate, hydrate, dehydrate, or anhydrous form of a salt or co-crystal form.

Accordingly, in a further aspect, the present invention provides a pharmaceutical composition comprising:

(a) an API having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

(b) a precipitation retardant; and

(c) an optional enhancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

(a) an API having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

(b) a precipitation retardant having an interfacial tension of less than 10 dyne/cm or a surface tension of less then 42 dyne/cm; and

(c) an optional enhancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

(a) an API having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

(b) a surfactant; and

(c) an optional enhancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

(a) an API having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

(b) a poloxamer having an interfacial tension of less than 10 dyne/cm or surface tension less then 42 dyne/cm; and

(c) an optional enhancer.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

(a) an API having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

(b) a surfactant; and

(c) a cellulose ester.

In a further aspect, the present invention provides a pharmaceutical composition comprising:

(a) an API having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

(b) a surfactant having an interfacial tension of less than 10 dyne/cm or surface tension less then 42 dyne/cm; and

(c) hydroxypropylcellulose (HPC) or hydroxypropylmethylcellulose (HPMC).

In a further aspect, the present invention provides a pharmaceutical composition comprising:

(a) an API having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

(b) a poloxamer; and

(c) hydroxypropylcellulose (HPC) or hydroxypropylmethylcellulose (HPMC).

In a further aspect, the present invention provides a pharmaceutical composition comprising:

(a) an API having low aqueous solubility or dissolution, preferably in gastric fluid conditions;

(b) a poloxamer having an interfacial tension of less than 10 dyne/cm or surface tension less then 42 dyne/cm; and

(c) hydroxypropylcellulose (HPC) or hydroxypropylmethylcellulose (HPMC).

In a further aspect, the present invention provides a pharmaceutical composition comprising

(a) celecoxib or valdecoxib;

(b) a poloxamer surfactant having an interfacial tension at a concentration of 0.1% of less than 10 dyne/cm or surface tension less then 42 dyne/cm; and

(c) hydroxypropylcellulose (HPC) or hydroxypropylmethylcellulose (HPMC).

In a further aspect, the present invention provides a process for producing a pharmaceutical composition for delivering a supersaturated concentration of a drug having low aqueous dissolution, preferably in gastric fluid conditions, which comprises intimately mixing together the components of the above aspects or elsewhere herein.

In a further aspect, the surfactant is at a concentration of less than 5 %, 4 %, 3 %, 2 %, 1 %, 0.9 %, 0.8 %, 0.7 %, 0.6 %, 0.5 %, 0.4 %, 0.3 %, 0.2 %, or 0.1 % or at a concentration of 0.1 % (w/w).

The present invention further provides a process for producing a pharmaceutical composition, which comprises:

(1) providing a plurality of containers;

(2) providing a plurality of excipient solutions;

(3) providing a plurality of compound solutions, each having dissolved therein a pharmaceutical compound;

(4) dispensing into each container one of the excipient solutions with one of the compound solutions so as to form an intimate mixture, a property of each mixture being varied in different containers;

(5) incubating the mixture;

(6) determining onset of solid-state nucleation or precipitation;

(7) selecting a pharmaceutical compound/excipient combination whereby onset of solid-state nucleation is retarded; and

(8) producing a pharmaceutical composition comprising the pharmaceutical compound/excipient combination.

Applicants found that it is possible to screen mixtures containing a pharmaceutical compound and an excipient in a rapid and simple manner so as to identify which properties of the pharmaceutical compound/excipient combination retard (inhibit) solid-state nucleation. The term "solid-state nucleation is used herein to refer to the initiation of solidification, whether amorphous or crystalline, but may be specified as being amorphous or crystalline. In this way, those excipients or other properties of the combination can be chosen for the production of a pharmaceutical composition in which the API remains in solution for a sufficient time after administration to a subject. In this way, pharmaceutical compositions which attain at least a minimum bioavailability of the API may be readily produced based on a straightforward in vitro screening.

Various properties of a pharmaceutical composition may affect the onset of solid-state nucleation or precipitation of the API . Such properties include the identity or amount of the excipient and the identity or amount of the pharmaceutical compound in the composition. Other properties may include the amount of other diluents or carriers such as salts or buffering compounds. The pharmaceutical compound itself may be screened in a variety of different forms if it is capable of polymorphism. Additionally, different salt, solvate, hydrate, co-crystal and other forms of the API may be screened in accordance with the invention.

The invention is readily applicable to screening a large variety of different excipients. Accordingly, in a preferred aspect, the present invention provides a process for producing a pharmaceutical composition, which comprises:

(1) providing a plurality of containers;

(2) providing a plurality of excipient solutions;

(3) providing a plurality of compound solutions, each having dissolved therein a pharmaceutical compound;

(4) dispensing into each container one of the excipient solutions with one of the compound solutions so as to form an intimate mixture, the excipient being varied in different containers;

(5) incubating the mixture;

(6) determining onset of solid-state nucleation or precipitation;

(7) selecting an excipient which is found to retard onset of solid-state nucleation or precipitation; and

(8) producing a pharmaceutical composition comprising the pharmaceutical compound and the selected excipient.

According to this embodiment, it is the excipient which is varied. Different excipients may be used in different containers and may be present as a single excipient or in a combination of a plurality of excipients, for example, a binary, ternary, tertiary or higher order combination.

In a further aspect, the present invention provides a pharmaceutical composition obtained by processes according to the invention. The pharmaceutical composition may comprise a further excipient, diluent or carrier. In a preferred aspect, the pharmaceutical composition is formulated for oral administration.

The invention further provides a method for assessing excipient-mediated retardation of solid-state nucleation or precipitation of a pharmaceutical compound, which method comprises:

(1) providing a plurality of containers;

(2) providing a plurality of excipient solutions;

(3) providing a plurality of compound solutions, each having dissolved therein a pharmaceutical compound;

(4) dispensing into each container one of the excipient solutions with one of the compound solutions so as to form an intimate mixture, a property of each mixture being varied in different containers;

(5) incubating the mixture;

(6) determining onset of solid-state nucleation or precipitation; and

(7) ranking the property of the mixture according to time of onset of solid-state nucleation or precipitation.

In a further aspect the present invention provides a method for screening excipients that retard solid-state nucleation or precipitation of a pharmaceutical compound, which method comprises:

(1) providing a plurality of containers;

(2) providing a plurality of excipient solutions;

(3) providing a plurality of compound solutions, each having dissolved therein a pharmaceutical compound;

(4) dispensing into each container one of the excipient solutions with one of the compound solutions so as to form an intimate mixture, the excipient being varied in different containers;

(5) incubating the mixture;

(6) determining onset of solid-state nucleation or precipitation; and

(7) ranking the excipient according to time of onset of solid-state nucleation or precipitation.

Generally speaking, the active pharmaceutical ingredient (API) is typically capable of existing as a supersaturated solution, preferably in an aqueous-based medium. The API may be a free acid, free base, co-crystal or salt, or a solvate, hydrate or dehydrate thereof. The invention is particularly applicable to pharmaceutical compositions comprising an API which, when in contact with a body fluid such as gastric juices or intestinal fluids, would be likely to precipitate or crystallize from solution in a nucleation event. Accordingly, the invention is particularly applicable to pharmaceutical compounds which may have relatively low solubility, or dissolution, as defined herein, when in contact with bodily fluids but possibly relatively high solubility, or dissolution, in appropriate *in vitro* conditions.

According to the invention, the compound solution is a solution wherein the compound is solubilized and may be a non-aqueous solution or an aqueous solution with a pH adjusted to accommodate the compound. For example, in order to achieve high solubility of the compound, a free base-type compound would be dissolved in aqueous solution at acidic pH whereas a free acid-type compound would be dissolved in an aqueous solution of basic pH. The compound solution may therefore be, and preferably is, a supersaturated solution when compared to water, gastric fluids or intestinal fluids. It would also be preferred for the excipient to be in a solution comprising water, usually deionised water, or another aqueous based solution. In one aspect, the mixture simulates gastric fluid (SGF) or intestinal fluids (SIF, 0.68% monobasic potassium phosphate, 1% pancreatin, and sodium hydroxide where the pH of the final solution is 7.5.) and in this aspect it is preferred that the excipient is added in a solution simulating those body fluids. Alternatively, further additives, usually in solution, may be added to form the mixtures creating an environment appropriate for the screening to be undertaken.

One advantage of the present invention is that the plurality of containers may be presented in a multiple well plate format or block and tube format such that at least 24, 48, 96, 384, or 1536 samples are assayed in parallel. Multiple block and tubes or multiwell plates may be assayed such that at least 1000, 3000, 5000, 7000, 10000, 20000, 30000, 40000, 50000, 60000, 70000, 80000, 90000, or 100000 total samples are assayed. This is advantageous because the process may be operated in a semi-automated or automated way using existing multiple well plate format-based apparatus. At least the step of dispensing may be performed with automated liquid handling apparatus. Accordingly, it is possible to operate the process as a high throughput screen. Additionally, using a multiple well plate format, the scale of the screening is relatively low. For example, each sample may contain less than 100 mg, 50mg, 25mg, 10, mg, 5 mg, 750 microg, 500 microg, 250, microg, 100 microg, 75 microg, 50 microg, 25 microg, 10 microg, 1 microg, 750ng, 500ng, 250ng, 100ng, or less than 50ng, depending on the API, sample size, etc. This, therefore, minimizes the amount of API which is needed to identify excipients or properties of the combination of pharmaceutical compound and excipient that retard onset of nucleation. In this way, improved speed and relatively low cost are advantages.

The intimate mixture formed in the process may be achieved by any conventional method, including the use of a mixer during or after dispensing of the solutions. Once the mixture has been formed, it is generally advantageous to incubate the mixture at a constant temperature, such as approximately 37 degrees C, to simulate *in vivo* conditions.

Measurement of onset of solid-state nucleation or precipitation may be determined for example, by measuring the light scattering of a mixture. This may be achieved by any conventional light scattering measurement, such as the use of a nephelometer. It is also possible to include a further step in which the crystallinity of the products of the solid-state nucleation or precipitation is determined. This step is conveniently performed before selecting the pharmaceutical compound/excipient combination for use in the pharmaceutical composition. Crystallinity may be determined, e.g., by birefringence screening.

Neither the light scattering measurement nor the birefringence screening are invasive measurement techniques. Advantageously, a portion or all of the sample solution does not need to be transferred to a second container and the containers or wells can be sealed with a transparent seal to allow use of these techniques.

In its most general aspect, the present invention relates to a pharmaceutical composition which includes an API having a low aqueous solubility or dissolution (as defined herein). Typically, low aqueous solubility in the present application refers to a compound having a solubility in water which is less than or equal to 10 mg/mL, when measured at 37 degrees C, and preferably less than or equal to 1 mg/mL. The invention relates more particularly to drugs which have a solubility of not greater than 0.1 mg/mL. The invention further relates to compounds that cannot be maintained as a supersaturated solution in gastric or intestinal fluid or in SGF or SIF. Such drugs include some sulfonamide drugs, such as the benzene sulfonamides, particularly those pyrazolylbenzenesulfonamides discussed above, which include COX-2 inhibitors. Disclosed herein are stable crystalline metal salts of pyrazolylbenzenesulfonamides such as celecoxib and valdecoxib. Such metal salts include alkali metal or alkaline earth metal salts, preferably sodium, potassium, lithium, calcium and magnesium salts.

It is preferred that the pharmaceutical composition is formulated for oral administration. Drugs according to the invention may be prepared in a form having

reduced time to onset of therapeutic effectiveness (the time when an effect for which the drug is administered can be identified or measured, e.g., the point in time when a reduction in fever or pain felt by a patient begins to occur) or increased bioavailability. The pharmaceutical compositions according to the invention are therefore particularly suitable for administration to human subjects.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a differential scanning calorimetry (DSC) thermogram of the sodium salt of celecoxib prepared by Example 1 between 50 degrees C and 110 degrees C.

Fig. 2 shows a thermogravimetric analysis (TGA) thermogram of the sodium salt of celecoxib prepared by Example 1, which was conducted from about 30 degrees C to about 160 degrees C.

Fig. 3 shows a PXRD diffractogram of the sodium salt of celecoxib prepared by Example 1.

Figs. 4A and 4B show pharmacokinetics in male Sprague-Dawley rats after 5 mg/kg oral doses of the celecoxib crystal form used in the marketed formulations and the sodium salt of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, as obtained following the protocol described in Example 4.

Fig. 5 shows the mean pharmacokinetic parameters (and standard deviations therefor) of celecoxib in the plasma of male dogs following a single oral or single intravenous dose of celecoxib or celecoxib sodium. The maximum serum concentration and bioavailability of orally-administered celecoxib sodium was about three- and two-fold greater, respectively, than a roughly equal dose of orally-administered celecoxib, and the maximum serum concentration of celecoxib sodium was reached 40% faster than for celecoxib.

Fig. 6 shows the mean concentrations of celecoxib in plasma following the administration of a single oral dose of celecoxib or celecoxib sodium or a single intravenous dose of celecoxib in male dogs.

Fig. 7 shows the effect of varying ratios of ethylene glycol to propylene glycol subunits in poloxamers on the concentration of celecoxib sodium in solution.

Fig. 8 shows the effect of different celluloses on the dissolution of various composition comprising equal weights of cellulose (hydroxypropylcellulose (HPC, 100,000 kDa), low-viscosity hydroxypropylmethylcellulose (ld HPMC, viscocity was 80-120 cps), high-viscosity hydroxypropylmethylcellulose (hd HPMC, viscosity was 15,000 cps), microcrystalline cellulose (Avicel PH200)), d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), and celecoxib sodium.

Fig. 9 shows the dissolution at 37 degrees C for compositions comprising various weight ratios of d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), hydroxypropylcellulose and celecoxib sodium.

Fig. 10 shows the dissolution profile of celecoxib sodium in simulated gastric fluid (SGF) from solid mixtures with excipients at room temperature. The legend indicates the excipient and the weight ratio of excipient to celecoxib sodium (if unmarked, 1:1). Excipients include polyvinylpyrrolidone (PVP), poloxamer 188 (P188), poloxamer 237 (P237), d-alpha-tocopherol polyethylene glycol-1000 succinate (vit E TGPS), and Gelucire^{TM} 50/13.

Fig. 11 shows the effect of Avicel microcrystalline cellulose and silica gel on the dissolution of mixtures of celecoxib sodium, d-alpha-tocopherol polyethylene glycol-1000 succinate (vit E TGPS), and hydroxypropylcellulose (HPC) mixtures in simulated gastric fluid (SGF) at 37 degrees C. The legend indicates the weight ratios of the components.

Fig. 12 shows the dissolution of celecoxib sodium in 5-times diluted simulated gastric fluid, with excipients including d-alpha-tocopherol polyethylene glycol-1000 succinate (vitamin E TGPS), hydroxypropylcellulose (HPC), and poloxamer 237. The legend indicates the weight ratios of the components.

Figs. 13A and 13B show the PXRD diffractogram and Raman spectrum, respectively, of the sodium salt of celecoxib prepared by the method of Example 6.

Fig. 14 shows a differential scanning calorimetry (DSC) thermogram of celecoxib lithium salt MO-116-49B.

Fig. 15 shows a thermogravimetric analysis (TGA) thermogram of celecoxib lithium salt MO-116-49B.

Fig. 16 shows the RAMAN spectrum of celecoxib lithium salt MO-116-49B.

Fig. 17 shows the PXRD diffractogram of celecoxib lithium salt MO-116-49B.

Fig. 18 shows a differential scanning calorimetry (DSC) thermogram of celecoxib potassium salt MO-116-49A.

Fig. 19 shows a thermogravimetric analysis (TGA) thermogram of celecoxib potassium salt MO-116-49A.

Fig. 20 shows the RAMAN spectrum of celecoxib potassium salt MO-116-49A.

Fig. 21 shows the PXRD diffractogram of celecoxib potassium salt MO-116-49A.

Fig. 22 shows a thermogravimetric analysis (TGA) thermogram of celecoxib potassium salt MO-116-55D.

Fig. 23 shows the RAMAN spectrum of celecoxib potassium salt MO-116-55D.

Fig. 24 shows the PXRD diffractogram of celecoxib potassium salt MO-116-55D.

Fig. 25 shows a thermogravimetric analysis (TGA) thermogram of celecoxib calcium salt MO-116-62A.

Fig. 26 shows the RAMAN spectrum of celecoxib calcium salt MO-116-62A.

Fig. 27 shows the PXRD diffractogram of celecoxib calcium salt MO-116-62A.

Fig. 28 shows the PXRD diffractogram of commercially-available celecoxib.

Fig. 29 shows the RAMAN spectrum of commercially-available celecoxib.

Fig. 30 shows crystal retardation time for celecoxib as a function of excipient in simulated gastric fluid (SGF).

Fig. 31 shows interfacial tension of selected PLURONIC excipients in water.

Fig. 32 shows dissolution of celecoxib sodium hydrate from compositions containing PLURONIC P123 and F127.

Fig. 33 shows dissolution of celecoxib sodium hydrate from PLURONIC P123, F127 and F87, in the presence of HPC.

Fig. 34 shows dissolution of celecoxib sodium hydrate using PLURONIC F127, HPC and a granulating fluid.

Fig. 35 shows dissolution of celecoxib sodium hydrate using PLURONIC F127 and HPC in a compact formulation.

Fig. 36 shows a flowchart outlining a process according to the invention.

Fig. 37 shows a platemap for an automated liquid dispenser.

Fig. 38 shows a trace of light scatter against time in an assay according to the invention.

Fig. 39 shows a thermogravimetric analysis (TGA) thermogram of a propylene glycol solvate of a celecoxib sodium salt.

Fig. 40 shows the PXRD diffractogram of a propylene glycol solvate of a celecoxib sodium salt.

Fig. 41 shows a thermogravimetric analysis (TGA) thermogram of a propylene glycol solvate of a celecoxib potassium salt.

Fig. 42 shows the PXRD diffractogram of a propylene glycol solvate of a celecoxib potassium salt.

Fig. 43 shows a thermogravimetric analysis (TGA) thermogram of a propylene glycol solvate of a celecoxib lithium salt.

Fig. 44 shows a thermogravimetric analysis (TGA) thermogram of the sodium salt propylene glycol trihydrate of celecoxib prepared by Example 21.

Fig. 45 shows a PXRD diffractogram of the sodium salt propylene glycol trihydrate of celecoxib prepared by Example 21a.

Fig. 46 shows a thermogravimetric analysis (TGA) thermogram of the sodium salt propylene glycoltrihydrate of celecoxib prepared by Example 21b.

Fig. 47 shows a PXRD diffractogram of the sodium salt propylene glycol trihydrate of celecoxib prepared by Example 21b.

Fig. 48 shows a differential scanning calorimetry (DSC) thermogram of the sodium salt isopropyl alcohol solvate of celecoxib prepared by Example 22.

Fig. 49 shows a thermogravimetric analysis (TGA) thermogram of the sodium salt isopropyl alcohol solvate of celecoxib prepared by Example 22, which was conducted from about 30° to about 160 degrees C.

Fig. 50 shows a PXRD diffractogram of the isopropyl alcohol solvate of celecoxib sodium salt prepared by Example 22.

Fig. 51 shows a PXRD diffractogram of the propylene glycol solvate of celecoxib lithium salt prepared by Example 20.

Fig. 52 shows a PXRD diffractogram of the celecoxib:nicotinamide co-crystals prepared by Example 23.

Fig. 53 shows a PXRD diffractogram of the hydrate of celecoxib sodium salt under 17 % RH prepared by Example 24.

Fig. 54 shows a PXRD diffractogram of the hydrate of celecoxib sodium salt under 31 % RH prepared by Example 24.

Fig. 55 shows a PXRD diffractogram of the hydrate of celecoxib sodium salt under 59 % RH prepared by Example 24.

Fig. 56 shows a PXRD diffractogram of the hydrate of celecoxib sodium salt under 74 % RH prepared by Example 24.

Fig. 57 shows a PXRD diffractogram of the hydrate of the propylene glycol solvate of celecoxib sodium salt under 17 % RH prepared by Example 24.

Fig. 58 shows a PXRD diffractogram of the hydrate of the propylene glycol solvate of celecoxib sodium salt under 31 % RH prepared by Example 24.

Fig. 59 shows a PXRD diffractogram of the hydrate of the propylene glycol solvate of celecoxib sodium salt under 59 % RH prepared by Example 24.

Fig. 60 shows a PXRD diffractogram of the hydrate of the propylene glycol solvate of celecoxib sodium salt under 74 % RH prepared by Example 24.

Fig. 61 shows PXRD diffractograms of multiple celecoxib sodium salt samples with various hydration states prepared by Example 25.

Fig. 62 shows a DSC thermogram of valdecoxib isopropanol solvate prepared by Example 26.

Fig. 63 shows a TGA thermogram of valdecoxib isopropanol solvate prepared by Example 26.

Fig. 64 shows a PXRD diffractogram of valdecoxib isopropanol solvate prepared by Example 26.

Fig. 65 shows a Raman spectrum of valdecoxib isopropanol solvate prepared by Example 26.

Fig. 66 shows a ^{1}H NMR spectrum of valdecoxib isopropanol solvate prepared by Example 26.

Fig. 67 shows a DSC thermogram of valdecoxib sodium salt prepared by Example 27.

Fig. 68 shows a TGA thermogram of valdecoxib sodium salt prepared by Example 27.

Fig. 69 shows a PXRD diffractogram of valdecoxib sodium salt prepared by Example 27.

Fig. 70 shows a Raman spectrum of valdecoxib sodium salt prepared by Example 27.

Fig. 71 shows an ^{1}H NMR spectrum of valdecoxib sodium salt prepared by Example 27.

DETAILED DESCRIPTION OF THE INVENTION

In its most general aspect, the present invention relates to a pharmaceutical composition that includes an API having a low aqueous solubility, e.g., in gastric fluid conditions. Typically, low aqueous solubility in the present application refers to a compound having a solubility in water which is less than or equal to 10mg/mL, when measured at 37 degrees C, and preferably less than or equal to 5mg/mL or 1mg/mL. "Low aqueous solubility" can further be defined as less than or equal to 900, 800, 700, 600, 500, 400, 300, 200 150 100, 90, 80, 70, 60, 50, 40, 30, 20 micrograms/mL, or further 10, 5 or 1 micrograms/mL, or further 900, 800, 700, 600, 500, 400, 300, 200 150, 100 90, 80, 70, 60, 50, 40, 30, 20, or 10 ng/mL, or less than 10 ng/mL when measured at 37 degrees C. Further aqueous solubility can be measured in simulated gastric fluid (SGF) rather than water. SGF (non-diluted) of the present invention is made by combining 1 g/L Triton X-100 and 2 g/L NaCl in water and adjusting the pH with 20mM HCl to obtain a solution with a final pH=1.7. The pH of the solution may also be specified as 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 3.5, 4, 4.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, or 12.

APIs which have a solubility of not greater than 0.1 mg/mL, including some sulfonamide drugs, such as the benzene sulfonamides, particularly those pyrazolylbenzenesulfonamides discussed above, which include COX-2 inhibitors, are included in the present invention. Disclosed herein are stable crystalline metal salts and co-crystals of pyrazolylbenzenesulfonamides such as celecoxib and valdecoxib. Such metal salts include alkali metal or alkaline earth metal salts, preferably sodium, potassium, lithium, calcium and magnesium salts.

In one aspect of the present invention, an API with low aqueous solubility is formulated with a precipitation retardant and, optionally, with a precipitation retardant enhancer. The precipitation retardant used in the present invention can be chosen from a wide range of surfactants (see e.g., Fig. 30). Embodiments include where the surfactant is non-ionic or where the surfactant is ionic. In embodiments of the present invention, the interfacial tension of the precipitation retardant (e.g., poloxamers) is less than 10 dyne/cm when measured as a concentration of 0.1 % w/w in water as compared to mineral oil at 25 degrees C and/or the surface tension of the precipitation retardant (e.g., poloxamers) is less than 42 dyne/cm when measured as a concentration of 0.1 % w/w in water. In other embodiments of the invention the interfacial tension is less than 15, 14, 13, 12, 11, 10, 9, 8, 7, or 6 dyne/cm or the surface tension is less than 45, 44, 43, 42, 41, 40, 39, 38, 37, 36, or 35 dyne/cm. In other embodiments, the surfactant is a poloxamer. A poloxamer comprises an ethylene oxide-propylene oxide block copolymer, which preferably has the structure $(PEG)_x$-$(PPG)_y$-$(PEG)_z$, where x, y and z are integers and x is usually equal to z. Preferred forms of poloxamers are those obtainable from BASF, as trademarked PLURONIC. The invention is not, however, limited to the PLURONIC series as similar poloxamers obtainable from other sources may be used. Examples of PLURONIC poloxamers according to the invention include PLURONIC L122, PLURONIC P123, PLURONIC F127 (Poloxamer 407), PLURONIC L72, PLURONIC P105, PLURONIC LP2, PLURONIC P104, PLURONIC F108 (Poloxamer 338), PLURONIC P103, PLURONIC L44 (Poloxamer 124), PLURONIC F68 (Poloxamer 188), and PLURONIC F87 (Poloxamer 237). A specific poloxamer and its corresponding PLURONIC, i.e., the generic and tradename, may be used interchangeably throughout.

In one embodiment, the invention provides a pharmaceutical composition comprising:

(a) an API; and

(b) a polyether block copolymer comprising an A-type linear polymeric segment joined at one end to a B-type linear polymeric segment, wherein the A-type segment is of relatively hydrophilic character, the repeating units of which contribute an average Hansch-Leo fragmental constant of about -0.4 or less and have molecular weight contributions between about 30 and about 500, wherein the B-type segment is of relatively

hydrophobic character, the repeating units of which contribute an average Hansch-Leo fragmental constant of about -0.4 or more and have molecular weight contributions between about 30 and about 500, wherein at least about 80% of the linkages joining the repeating units for each of the polymeric segments comprise an ether linkage. In a preferred first embodiment, the polyether block copolymer is selected from the group consisting of polymers of formulas:

A-B-A', A-B, B-A-B', or $L(R^1)(R^2)(R^3)(R^4)$

(III) (IV) (V) (VI)

wherein A and A' are A-type linear polymeric segments, B and B' are B-type linear polymeric segments, and R^1, R^2, R^3 and R^4 are either block copolymers of formulas (III), (IV) or (V) or hydrogen and L is a linking group, with the proviso that no more than two of R^1, R^2, R^3 or R^4 are hydrogen.

In another embodiment, the composition includes micelles of the block copolymer or forms micelles of the block copolymers during the course of administration or subsequent thereto. Preferably, at least about 0.1 % of the biological agent is incorporated in the micelles, more preferably, at least about 1 % of the biological agent, yet more preferably, at least about 5 % of the biological agent.

In another embodiment, the hydrophobic percentage of the copolymer of the composition is at least about 50 % more preferably, at least about 60 %, yet more preferably 70 %.

In another embodiment, the hydrophobic weight of the copolymer is at least about 900, more preferably, at least about 1700, yet more preferably at least about 2000, still more preferably at least about 2300.

In other embodiments, the hydrophobic weight is at least about 2000 and the hydrophobic percentage is at least about 20 %, preferably 35 %; or the hydrophobic weight is at least about 2300 and the hydrophobic percentage is at least about 20 %, preferably 35 %.

The optional third component of the pharmaceutical composition according to the present invention comprises a precipitation retardant enhancer. An enhancer is a compound capable of increasing the effectiveness of the precipitation retardant in

inhibiting, preventing or at least reducing the extent of precipitation of a drug of low aqueous solubility, usually when diluted such as following oral administration. In one embodiment the enhancer does not act as a precipitation retardant alone. In another embodiment the enhancer has no effect or a negative effect in an in vitro precipitation assay, but increases the effectiveness of the precipitation retardant in an in vivo or in vitro dissolution assay. Cellulose esters, such as hydroxypropyl cellulose, are particularly useful enhancers according to the present invention. Cellulose esters vary in the chain length of their cellulosic backbone and consequently, vary in their viscosities as measured for example at a 2% by weight concentration in water at 20 degrees C. Lower viscosities are normally preferred to higher viscosities in the present invention. In embodiments of the present invention the cellulose ester, such as HPC, has a viscosity, 2% in water, of about 100 to about 100,000 cP or about 1000 to about 15,000 cP. In other embodiments the viscosity is less than 1,500,000, 1,000,000, 500,000, 100,000, 75,000, 50,000, 35,000, 25,000, 20,000, 17,500, 15,000, 12,500. 11,000, 10,500, 9,000, 8,000, 7,000, 6,000, 5,000, 4,000, 3,000, 2,000, 1,000, 750, 500, or 250 cP, or has a viscosity in a range selected from any two preceding integers.

Enhancers are also useful in delaying the T_{max} and/or increasing the amount of time the API concentration is above ½ T_{max}, thus acting to smooth out a curve of blood serum concentration vs. time. Preferred enhancers increase the amount of time the API concentration is above ½ T_{max} by 25%, 50%, 75%, 100%, three fold or more than three fold. In a preferred embodiment, the composition has both a reduced time to T_{max} and remains at ½ T_{max} longer than the free acid or in the same composition except the salt or co-crystal is replaced by the free acid.

The ratio of component a:b:c (API: precipitation retardant;enhancer) as exemplified herein is approximately 1:1:1 (+/- 0.2 for the precipitation retardant and enhancer). However, the ratio can be adjusted to suit the application. For example, the amount of precipitation retardant or enhancer may need to be decreased, and even decreased below the optimum concentration in order to decrease the amount of excipients in the administered form of the composition, such as a tablet or capsule. In one embodiment the unit dosage form comprises an amount of precipitation retardant (surfactant) that is at or above an amount needed for the retardant to reach its critical micell concentration (CMC)

in H_20 or SGF. It is noted the poloxamers may not form true micells but do form analogous structures which are considered micells for the purpose of the present invention.

The composition may further comprise a pharmaceutically-acceptable diluent, excipient or carrier and such additional components are discussed in further detail below. One such additional component comprises a granulating fluid-like liquid, such as poloxamer 124, PEG 200 or PEG 400, that forms an intimate contact between the API, precipitation retardant and optional enhancer by binding or partially dissolving them. Preferably the composition remains in a solid, semi-solid or paste, although an embodiment is drawn to wherein the composition is at least 25%, 50%, 75% or nearly or fully dissolved Any pharmaceutically acceptable liquid may be used as long as it does not cause conversion of the salt or co-crystal form to the free form in the solid state. Some non-limiting examples include methanol, ethanol, isopropanol, higher alcohols, propylene glycol, ethyl caprylate, propylene glycol laurate, PEG, diethyl glycol monoethyl ether (DGME), tetraethylene glycol dimethyl ether, triethylene glycol monoethyl ether, and polysorbate 80. The presence of the granulating fluid-like liquid increases the dissolution of the API, possibly by delaying the contact between the API and the dissolution medium until the surfactant dissolves to a significant extent, thus delaying precipitation. The use of a granulating fluid-like liquid is particularly useful when the API and precipitation retardant are solids.

As an alternative embodiment to increase supersaturation of the API, the pharmaceutical composition is in the form of a compact whereby, during the process of producing the pharmaceutical composition, the components are compacted together. Compaction may perform a similar role to that performed by the granulating fluid. Retarded dissolution or a smoothing out of the curve of blood serum concentration vs. time may be limited, if required, by using a disintegrant in the compact.

In a further embodiment the API and precipitation retardant (and optional enhancer), forms a paste or non-aqueous solution when mixed. An adherent mass of components may be produced if a paste is used, which is thought to delay dissolution of the API by allowing the surfactant to dissolve first. This is thought to promote supersaturation of the API.

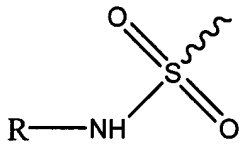
Normally the compounds of the present invention are intimately associated as a pharmaceutical composition. An "intimate association" in the present context includes, for example, the pharmaceutical admixed with the precipitation retardant, the pharmaceutical embedded or incorporated in the retardant, the compound forming a coating on particles of the pharmaceutical or vice versa, and a substantially homogeneous dispersion of the pharmaceutical throughout the compounds.

Where the pharmaceutical composition includes a COX-2 inhibitor, a method of treating a subject is provided in a further aspect of the invention, in which the subject may be suffering from pain, inflammation, cancer or pre-cancer such as intestinal or colonic polyps. The method comprises administering to the subject a pharmaceutical composition as described herein.

It is preferred that the pharmaceutical composition is formulated for oral administration. Drugs according to the invention may be prepared in a form having a decreased time to onset of therapeutic effectiveness and an increased bioavailability. The pharmaceutical compositions according to the invention are particularly suitable for administration to human subjects.

The methods and compositions of the present invention relate to improving solubility, dissolution and bioavailability of pharmaceuticals. The present invention further relates to improving the performance of pharmaceutical compounds that initially dissolve but then precipitate or recrystallize in gastric fluid conditions.

Further embodiments relate to pharmaceuticals with an aminosulfonyl functional group. The term "aminosulfonyl functional group" herein refers to a functional group having the following structure (VII):



(VII)

Wherein the wavy line represents a bond by which the functional group is attached to the rest of the drug molecule; and R is hydrogen or a substituent that preserves ability of polyethylene glycol or a polyethylene glycol degradation product to react with the amino

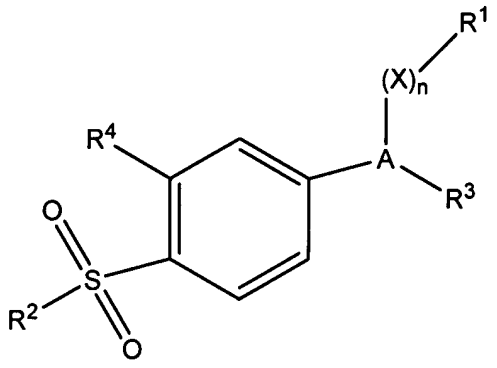
group adjacent to R to form an addition compound. Illustrative examples of such substituents include partially unsaturated hereocyclyl, hereoaryl, cycloalkenyl, aryl, alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, phenyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, hydroxyl, alkoxyalkyloxyalkyl, haloalkylsulfonyloxy, carboxyalkoxyalkyl, cycloalkylalkyl, alkynyl, heterocyclyloxy, alkylthio, cycloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, heteroarylcarbonyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-Narylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylamincoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsufinyl, alkylsufonyl, etc.

Non-limiting illustrative examples of aminosulfonyl-comprising drugs include ABT-751 of Eisai (N-(2-(4-hydroxyphenyl)amino)-3-pyridyl)4-methoxybenzenesulfonamide); alpiropride; amosulalol; amprenavir; amsacrine; argatroban; asulacrine; azosemide; BAY-38-4766 of Bayer (N-[4-[[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]amino]phenyl]-3-hyrdroxy-2,2-dimethylpropanamide); bendroflumethiazide; BMS-193884 of Bristol Myers Squibb (N-(3,4-dimethyl-5-isoxazolyl)-4^1-(2-oxazolyl)-[1,1^1-biphenyl]-2-sulfonamide); bosentan; bumetide; celecoxib; chlorthalidone; delavirdine; deracoxib dofetilide; domitroban; dorzolamide; dronedarone; E-7070 of Eisai (N-(3-chloro-1H-indol-7-yl)-1, 4-benzene-disulfonamide); EF-7412 of Schwartz Pharma (N-3-[4-[4-(tetrahydro-1,3-dioxo-1H-pyrrolo[1,2-c]imidazol-2(3H)-yl)butyl]-1-piperazinyl]phenyl]ethanesulfonamide); fenquizone; furosemide; glibenclamide; gliclazide; glimepiride; glipentide; glipizide; gliquidone; glisolamide; GW-8510 of Glaxo SmithKline (4-[[6,7-dihydro-7-oxo-8H-pyrrolo[2,3-g]benzothiazol-8-ylidene)methyl]amino]-N-2-pyridinylbenzenesulfonamide); GYKI-16638 of Ivax (N-[4-[2-[[2-(2,6-dimethoxylphenoxy)-1-methlethyl]methylamino]ethyl]phenyl] methanesulfonamide); HMR-1098 of Aventis (5-chloro-2-methoxy-N-[2-[4-methoxy-3[[[(methylamino)thioxomethyl]amino]sulfonyl]phenyl]ethyl]benzamide);

hydrochlorothiazide; ibutilide; indapamide; IS-741 of Ishihara (N-[2-[(ethylsufonyl) amino]-5-(trifluoromethyl)-3-pyridinyl]cyclohexanecarboxamide); JTE-522 of Japan Tobacco (4-(4-cyclohexyl-2-methyl-5-oxazolyl)-2-fluorobenzenesulfonamide); KCB-328 of Chugai (N-[3-amino-4-[2-[[2-3,4-dimethoxyphenyl)ethyl]methylamino] ethoxy]phenyl]methanesulfonamide); KT2-962 of Kotobuki (3-[4-[[(4-chlorophenyl) sulfonyl]amino]butyl]-6-(1-methylethyl)-1-azulene sulfonic acid); levosulpiride; LY-295501 (N-[[(3,4-dichlorophyenyl)amino]carbonyl]-2,3-dihydro-5-benzofuransulfonamide) and LY-404187 (N-2-(4-(4-cyanophenyl)phenyl)propyl-2-propanesulfonamide) of Eli Lilly; metolazone; naratriptan; nimesulide; NS-49 of Nippon ((R)-N-[3-(2-amino-1-hydroxyethyl)-4-flourophenyl]methanesulfonamide); ONO-8711 of Ono ((5Z)-6-[(2R,3S)-3-[[[(4-chloro-2-methylphenyl)sulfonyl]amino]methyl]bicyclo[2.2.2]oct-2-yl]-5-hexenoic acid); piretanide; PNU-103657of Pharmacia (1-[5-methanesulfonamidoindol-2-ylcarbonyl]-4-(N-methyl-N-(3-(2-methylpropyl)-2-pyridinyl)amino)piperidine); polythiazide; ramatroban; RO-61-1790 of Hoffmann LaRoche (N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-[2-(1H-tetrazol-5-yl)-4-pyridinyl]-4-pyrimidinyl]-5-methyl-2-pyridinesulfonamide); RPR-130737 (4-hydroxy-3-[2-oxo-3(S)-[5-(3-pyridyl)thiophen-2-ylsulfonamido]pyrrolidin-1-ylmethyl]benzamide) and RPR-208707 of Aventis; S-18886 (3-[(6-(4-chlorophenylsulfonylamino)-2-methyl-5,6,7,8-tetrahydronaphth]-1-yl)propionic acid) and S-32080 (3-[6-(4-chlorophenylsulfonylamido)-2-propyl-3-(3pyridyl-methyl)-5,6,7,8-tetrahydronaphthalen-1-yl]propionic acid) of Server; S-36496 of Kaken (2-sulfonyl-[N-(4-chlorophenyl)sulfonylamino-butyl-N-[(4-cyclobutylthiazol-2-yl)ethenylphenyl-3-yl-methyl]]aminobenzoic acid); sampatrilat;SB-203208 of Glaxo Smith Kline (L-phenylalanine, b-methyl-,(4aR,6S,7R,7aS)-4-(aminocarbonyl)-7-[[[[[(2S,3S)-2-amino-3-methyl-l-oxopentyl]amino]sulfonyl]acetyl]amino]-7-carboxy-2,4a,5,6,7,7a-hexahydro-2-methyl-1H-cyclopenta[c]pyridine-6yl ester, (bS)-); SE-170 of DuPont (2-(5-amidino-1H-indol-3-yl)N-[2'-(aminosulfonyl)-3-bromo(1,1'biphenyl)-4-yl]acetamide); sivelestat; SJA-6017 of Senju (N-(4-flourophenylsulfonyl)-L-valyl-L-leucinal); SM-19712 of Sumitomo (4-chloro-N-[[(4-cyano-3-methyl-1-phenyl-1H-pyrazol-5-yl) amino] carbonyl]benzenesulfonamide); sonepiprazole; sotalol; sulfadiazine; sulfaguanole; sulfasalazine; sulpride; sulprostone; sumatriptan; T-614 of Toyama (N-[3-(formylamino)-

4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide); T-138067 (2,3,4,5,6-pentafluoro-N-(3-flouro-4-methoxyphenyl)benzenesulfonamide) and T-900607 (2,3,4,5,6-pentafluoro-N-3-ureido-4-methoxyphenyl)benzenesulfonamide) of Tularik; TAK-661 of Takeda (2,2-dimethyl-3-[[7-(1-methylethyl)[1,2,4]triazolo[1,5-b]pyridazin-6-yl]oxy]-1-propanesulfonamide); tamsulosin; tezosentan; tipranavir; tirofiban; torasemide; trichloromethiazide; tripamide; valdecoxib; veralipride; xipamide; Z-335 of Zeria (2-[2-(4-chlorophenylsulfonylaminomethyl)indan-5-yl]acetic acid); zafirlukast; zonisamide; and salts thereof.

In a preferred embodiment, the aminosulfonyl-comprising drug is a selective COX-2 inhibitory drug of low water solubility. Suitable selective COX-2 inhibitory drugs are compounds having the formula (VIII):



(VIII)

wherein:

A is a substituent selected from partially unsaturated or unsaturated heterocyclic and partially unsaturated or unsaturated carbocyclic rings, preferably a heterocyclic group selected from pyrazolyl, furanoyl, isoxazolyl, pyridinyl, cyclopentenonyl and pyridazinonyl groups;

X is O, S or CH_2;

n is 0 or 1;

R^1 is at least one subsituent selected from heterocyclyl, cycloalkyl, cycloalkenyl and aryl, and is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl,

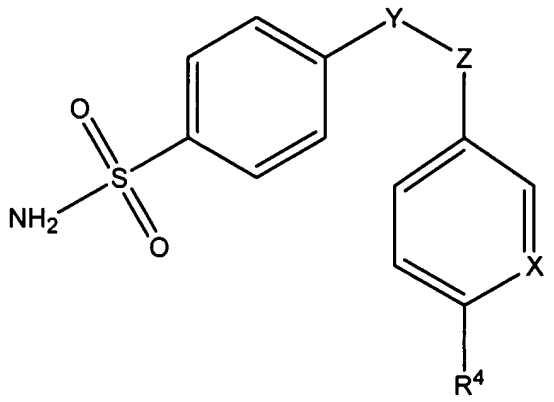
haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsufinyl, halo, alkoxy and alkylthio;

R^2 is NH_2 group;

R^3 is one or more radicals selected from hydrido, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclyalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl and N-alkyl-N-arylaminosulfonyl, R^3 being optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsufinyl, halo, alkoxy and alkylthio; and

R^4 is selected from hydrido and halo.

Particularly suitable selective COX-2 inhibitory drugs are compounds having the formula (IX):



(IX)

where R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five-to-six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl, or halomethyl groups. Preferred such five-to six-membered rings are cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

Illustratively, compositions of the invention are suitable for celecoxib, deracoxib, valdecoxib and JTE-522, more particularly celecoxib, paracoxib and valdecoxib. Other examples of suitable compositions include Acetazolamide CAS Registry Number: 59-66-5, Acetohexamide CAS Registry Number: 968-81-0, Alpiropride CAS Registry Number: 81982-32-3, Althiazide CAS Registry Number: 5588-16-9, Ambuside CAS Registry Number: 3754-19-6,Amidephrine CAS Registry Number: 3354-67-4, Amosulalol CAS Registry Number: 85320-68-9, Amsacrine CAS Registry Number: 51264-14-3, Argatroban CAS Registry Number: 74863-84-6, Azosemide CAS Registry Number: 27589-33-9, Bendroflumethiazide CAS Registry Number: 73-48-3, Benzthiazide CAS Registry Number: 91-33-8, Benzylhydrochlorothiazide CAS Registry Number: 1824-50-6, *p*-(Benzylsulfonamido)benzoic Acid CAS Registry Number: 536-95-8, Bosentan CAS Registry Number: 147536-97-8, Brinzolamide CAS Registry Number: 138890-62-7 Bumetanide CAS Registry Number: 28395-03-1, Butazolamide CAS Registry Number: 16790-49-1, Buthiazide CAS Registry Number: 2043-38-1, Carbutamide CAS Registry Number: 339-43-5, Chloraminophenamide CAS Registry Number: 121-30-2, Chlorothiazide CAS Registry Number: 58-94-6,Chlorpropamide CAS Registry Number: 94-20-2, Chlorthalidone CAS Registry Number: 77-36-1, Clofenamide CAS Registry Number: 671-95-4, Clopamide CAS Registry Number: 636-54-4, Clorexolone CAS Registry Number: 2127-01-7, Cyclopenthiazide CAS Registry Number: 742-20-1, Cyclothiazide CAS Registry Number: 2259-96-3, Daltroban CAS Registry Number: 79094-20-5, Delavirdine CAS Registry Number: 136817-59-9, Diazoxide CAS Registry Number: 364-98-7, Dichlorphenamide CAS Registry Number: 120-97-8, Disulfamide CAS Registry Number: 671-88-5, Dofetilide CAS Registry Number: 115256-11-6, Domitroban CAS Registry Number: 112966-96-8, Dorzolamide CAS Registry Number: 120279-96-1, Ethiazide CAS Registry Number: 1824-58-4, Ethoxzolamide CAS Registry

Number: 452-35-7, Fenquizone CAS Registry Number: 20287-37-0, Flumethiazide CAS Registry Number: 148-56-1, N^2-Formylsulfisomidine CAS Registry Number: 795-13-1, Furosemide CAS Registry Number: 54-31-9, Glibornuride CAS Registry Number: 26944-48-9, Gliclazide CAS Registry Number: 21187-98-4, Glimepiride CAS Registry Number: 93479-97-1, Glipizide CAS Registry Number: 29094-61-9, Gliquidone CAS Registry Number: 33342-05-1, Glisoxepid CAS Registry Number: 25046-79-1, N^4-Beta-D-Glucosylsulfanilamide CAS Registry Number: 53274-53-6, Glyburide CAS Registry Number: 10238-21-8, Glybuthiazol(e) CAS Registry Number: 535-65-9, Glybuzole CAS Registry Number: 1492-02-0, Glyhexamide CAS Registry Number: 451-71-8, Glymidine CAS Registry Number: 339-44-6, Glypinamide CAS Registry Number: 1228-19-9, Hydrochlorothiazide CAS Registry Number: 58-93-5, Hydroflumethiazide CAS Registry Number: 135-09-1, Ibutilide CAS Registry Number: 122647-31-8, Indapamide CAS Registry Number: 26807-65-8, Mafenide CAS Registry Number: 138-39-6, Mefruside CAS Registry Number: 7195-27-9, Methazolamide CAS Registry Number: 554-57-4, Methyclothiazide CAS Registry Number: 135-07-9, Metolazone CAS Registry Number: 17560-51-9, Naratriptan CAS Registry Number: 121679-13-8, Nimesulide CAS Registry Number: 51803-78-2, Noprylsulfamide CAS Registry Number: 576-97-6, Paraflutizide CAS Registry Number: 1580-83-2, Phenbutamide CAS Registry Number: 3149-00-6, Phenosulfazole CAS Registry Number: 515-54-8, Phthalylsulfacetamide CAS Registry Number: 131-69-1, Phthalylsulfathiazole CAS Registry Number: 85-73-4, Sulfacetamide CAS Registry Number: 144-80-9, Sulfachlorpyridazine CAS Registry Number: 80-32-0, Sulfachrysoidine CAS Registry Number: 485-41-6, Sulfacytine CAS Registry Number: 17784-12-2, Sulfadiazine CAS Registry Number: 68-35-9, Sulfadicramide CAS Registry Number: 115-68-4, Sulfadimethoxine CAS Registry Number: 122-11-2, Sulfadoxine CAS Registry Number: 2447-57-6, Piretanide CAS Registry Number: 55837-27-9, Polythiazide CAS Registry Number: 346-18-9, Quinethazone CAS Registry Number: 73-49-4 Ramatroban CAS Registry Number: 116649-85-5, Salazosulfadimidine CAS Registry Number: 2315-08-4, Sampatrilat CAS Registry Number: 129981-36-8, Sematilide CAS Registry Number: 101526-83-4, Sivelestat CAS Registry Number: 127373-66-4, Sotalol CAS Registry Number: 3930-20-9, Soterenol CAS Registry Number: 13642-52-9, Succinylsulfathiazole CAS Registry Number: 116-43-8,

Suclofenide CAS Registry Number: 30279-49-3, Sulfabenzamide CAS Registry Number: 127-71-9, Sulfaethidole CAS Registry Number: 94-19-9, Sulfaguanole CAS Registry Number: 27031-08-9, Sulfalene CAS Registry Number: 152-47-6, Sulfaloxic Acid CAS Registry Number: 14376-16-0, Sulfamerazine CAS Registry Number: 127-79-7, Sulfameter CAS Registry Number: 651-06-9, Sulfamethazine CAS Registry Number: 57-68-1, Sulfamethizole CAS Registry Number: 144-82-1, Sulfamethomidine CAS Registry Number: 3772-76-7, Sulfamethoxazole CAS Registry Number: 723-46-6, Sulfamethoxypyridazine CAS Registry Number: 80-35-3, Sulfametrole CAS Registry Number: 32909-92-5, Sulfamidochrysoidine CAS Registry Number: 103-12-8, Sulfamoxole CAS Registry Number: 729-99-7, Sulfanilamide CAS Registry Number: 63-74-1, 4-Sulfanilamidosalicylic Acid CAS Registry Number: 6202-21-7, N^4-Sulfanilylsulfanilamide CAS Registry Number: 547-52-4, Sulfanilylurea CAS Registry Number: 547-44-4, *N*-Sulfanilyl-3,4-xylamide CAS Registry Number: 120-34-3, Sulfaperine CAS Registry Number: 599-88-2, Sulfaphenazole CAS Registry Number: 526-08-9, Sulfaproxyline CAS Registry Number: 116-42-7, Sulfapyrazine CAS Registry Number: 116-44-9, Sulfapyridine CAS Registry Number: 144-83-2, Sulfarside CAS Registry Number: 1134-98-1, Sulfasalazine, CAS Registry Number: 599-79-1, Sulfasomizole CAS Registry Number: 632-00-8, Sulfasymazine CAS Registry Number: 1984-94-7, Sulfathiazole CAS Registry Number: 72-14-0, Sulfathiourea CAS Registry Number: 515-49-1, Sulfisomidine CAS Registry Number: 515-64-0, Sulfisoxazole CAS Registry Number: 127-69-5, Sulpiride CAS Registry Number: 15676-16-1, Sulprostone CAS Registry Number: 60325-46-4, Sulthiame CAS Registry Number: 61-56-3, Sumatriptan CAS Registry Number: 103628-46-2, Tamsulosin CAS Registry Number: 106133-20-4, Taurolidine CAS Registry Number: 19388-87-5, Teclothiazide CAS Registry Number: 4267-05-4, Tevenel® CAS Registry Number: 4302-95-8, Tirofiban CAS Registry Number: 144494-65-5,

Tolazamide CAS Registry Number: 1156-19-0, Tolbutamide CAS Registry Number: 64-77-7, Tolcyclamide CAS Registry Number: 664-95-9, Torsemide CAS Registry Number: 56211-40-6, Trichlormethiazide CAS Registry Number: 133-67-5, Tripamide CAS Registry Number: 73803-48-2, Veralipride CAS Registry Number: 66644-81-3,

Xipamide CAS Registry Number: 14293-44-8, Zafirlukast CAS Registry Number: 107753-78-6, Zonisamide CAS Registry Number: 68291-97-4.

In a particularly preferred embodiment, the pharmaceutical compositions of the present invention comprise a salt of celecoxib or valdecoxib, (e.g., sodium, lithium, potassium, magnesium, or calcium salt). The salt may be significantly more soluble in water than the free acid form of the API. Due to the high pK_as of celecoxib and underivatized valdecoxib(approximately 11), salts only form under strongly basic conditions. Typically, more than about one equivalent of a base is required to convert celecoxib and valdecoxib totheir respective salt forms. A suitable aqueous solution for converting either free acid to a salt has a pH of about 11.0 or greater, about 11.5 or greater, about 12 or greater, or about 13 or greater. Typically, the pH of such a solution is about 12 to about 13. Although celecoxib and valdecoxib are preferred embodiments, the invention includes other pharmaceutical drugs with pK_as greater than 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, or 13. The drugs may normally be in a neutral form or a salt form may already exist.

Salts of the pharmaceutical, such as celecoxib and valdecoxib, are formed by reaction of the pharmaceutical with an acceptable base. Acceptable bases include, but are not limited to, metal hydroxides and alkoxides. Metals include alkali metals (sodium, potassium, lithium, cesium), alkaline earth metals (magnesium, calcium), zinc, aluminum, and bismuth. Alkoxides include methoxide, ethoxide, n-propoxide, isopropoxide and t-butoxide. Additional bases include arginine, procaine, and other molecules having amino or guanidinium moieties with sufficiently high pK_a's (e.g., pK_a's greater than about 11, pK_a's greater than about 11.5, or pK_a's greater than about 12), along with compounds having a carbon-alkali metal bond (e.g., t-butyl lithium). Sodium hydroxide and sodium ethoxide are preferred bases. The amount of base used to form a salt is typically about one or more, about two or more, about three or more, about four or more, about five or more, or about ten or more equivalents relative to the pharmaceutical. Preferably, about three to about five equivalents of one or more bases are reacted with the pharmaceutical to form a salt.

A pharmaceutical salt can be transformed into a second pharmaceutical salt by transmetallation or another process that replaces the cation of the first pharmaceutical salt. In one example, a sodium salt of the pharmaceutical is prepared and is subsequently

reacted with a second salt such as an alkaline earth metal halide (e.g., $MgBr_2$, $MgCl_2$, $CaCl_2$, $CaBr_2$), an alkaline earth metal sulfate or nitrate (e.g., $Mg(NO_3)_2$, $Mg(SO_4)_2$, $Ca(NO_3)_2$, $Ca(SO_4)_2$), or an alkaline metal salt of an organic acid (e.g. calcium formate, magnesium formate, calcium acetate, magnesium acetate, calcium propionate, magnesium propionate) to form an alkaline earth metal salt of the pharmaceutical.

In a preferred embodiment of the present invention, the pharmaceutical salts are substantially pure. A salt that is substantially pure can be greater than about 80% pure, greater than about 85% pure, greater than about 90% pure, greater than about 95% pure, greater than about 98% pure, or greater than about 99% pure. Purity of a salt can be measured with respect to the amount of salt (as opposed to unreacted neutral pharmaceutical or base) or can be measured with respect to a specific polymorph, co-crystal, solvate, desolvate, hydrate, dehydrate, or anhydrous form of a salt.

A pharmaceutical salt as described herein may be significantly more soluble in water than the existing neutral form, such as the free acid alone or the presently-marketed neutral celecoxib (CELEBREX), and is typically at least about twice, at least about three times, at least about five times, at least about ten times, at least about twenty times, at least about fifty times, or at least about one hundred times more soluble in water or SGF than the neutral form. CELEBREX is marketed by Pfizer Inc. and G. D. Searle & Co. (Pharmacia Corporation), and described on pages 2676-2680 and 2780-2784 of the 2002 edition of the Physicians Desk Reference (also referred to herein as presently-marketed celecoxib). The reference compounds to the present invention herein can refer to the free acid neutral celecoxib, either crystalline or amorphous, CELEBREX™, the free acid neutral valdecoxib, either crystalline or amorphous, or BEXTRA™. The solubility depends on whether the salt is tested alone, or as a formulation further comprising the precipitation retardants and enhancers of the invention.

After dissolution, typically in an aqueous or partially-aqueous solution (e.g., where one or more polar organic solvents are a co-solvent), the salt can be neutralized by an acid or by dissolved gases such as carbon dioxide. Typically, the pH of such a solution is 11 or less, 10 or less, or 9 or less. Neutralizing the salt results in precipitation of an amorphous or metastable crystalline form of neutral celecoxib. Typically, neutralizing a pharmaceutical salt includes protonating the majority of negatively charged anions. For

celecoxib, protonation results in the formation of amorphous and/or metastable crystalline celecoxib, which are "neutral" (i.e., predominantly uncharged). Preferably, the neutral pharmaceutical (including amorphous and/or metastable crystalline forms thereof, such as celecoxib) comprises 10% mol or less of charged molecules. For example, at about pH 2 (e.g., about the pH of the stomach interior), solutions of the sodium salt of celecoxib precipitate immediately as an amorphous form of neutral celecoxib. The amorphous form converts to a neutral metastable crystalline form, which subsequently becomes the stable, needle-like, insoluble form of neutral celecoxib. For example, amorphous neutral celecoxib formed from the salts of the present invention, e.g., the sodium salt of Example 1, converts to metastable crystalline neutral celecoxib over about 5 to about 10 minutes. Amorphous neutral celecoxib can be characterized by a lack of regular crystal structure, while metastable crystalline neutral celecoxib can be distinguished from typical crystalline neutral celecoxib by the PXRD pattern of isolated material.

Amorphous and metastable crystalline forms of neutral celecoxib are more soluble and likely more readily absorbed by a subject than stable crystalline forms of neutral celecoxib, because the energy required for a drug molecule to escape from a stable crystal is greater than the energy required for the same drug molecule to escape from a non-crystalline, amorphous form or a metastable crystalline form. However, the instability of neutral amorphous and neutral metastable crystalline forms makes them difficult to formulate as pharmaceutical compositions. As is described in U.S. Publication No. 2002/0006951, the teachings of which are incorporated herein by reference in their entirety, without stabilization by a crystallization inhibitor, such as a polymer, amorphous neutral celecoxib converts back to a stable, insoluble crystalline form of free neutral celecoxib. These teachings are incomplete and fall far short of the present invention however, as we have surprisingly found that far superior formulations can be made from the combination of a salt or co-crystal, precipitation retardant, and an optional enhancer. Whereas others have focused on the initial solubilization of celecoxib, the present invention is equally concerned with dissolution and precipitation of the drug (See e.g., WO 02/102376 and WO 01/78724). Moreover, until now, no one has disclosed a salt of celecoxib and the vital role it plays in dissolution and precipitation. Further, no one has taught the addition of an enhancer to a precipitation retardant.

Further aspects of the invention relate to liquid formulations of compounds of the present invention (e.g. celecoxib). In these aspects, the drug is solubilized either directly with the precipitation retardant or with a solubilizer or solvent. Preferred solubilizers are polyethylene oxides. More preferably, the polyethylene oxide is a surfactant. Preferred ethylene oxides comprise the functional group $-(C_2H_4O)_n-$ where $n \geq 2$. Other preferred polyethylene oxides are poloxamers having the general formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$ where $a \geq 2$, where $a \geq 3$, where $a \geq 2$ and $b \geq 30$, where $a \geq 2$ and $b \geq 4$, where $a \geq 2$ and $b \geq 50$, where $a \geq 2$ and $b \geq 60$.

An aminosulfonyl containing API (celecoxib) was crystallized with molecules comprising at least two oxygen atoms (e.g., ether groups) to examine the physical interactions involved in precipitation retardation by the precipitation retardant. From these results, in one aspect of the present invention the precipitation retardant compounds, preferably surfactants, have the following physical properties or characteristics: The retardant molecule comprises at least one, preferably two, 10, 25, 40, 50, 60, 80, 100 or more functional interacting groups, wherein a functional interacting group comprises two oxygen atoms, with each of the two oxygen atoms interacting (e.g., hydrogen bonding) with the API. Preferably the two oxygen atoms interact with the aminosulfonyl group of the API. Preferably the aminosulfonyl group is $-SO_2NH_2$. The two interacting oxygen atoms are preferably separated by between about 3.6 angstroms to about 5.8 angstroms, about 3.9 angstroms to about 5.5 angstroms, 4.3 to about 5.2 angstroms, 4.6 to about 5.0 angstroms, or about 4.7 to about 4.9 angstroms. In one embodiment, the two oxygen atoms are separated by at least three atoms. In another embodiment, the two oxygen atoms are separated by 5 atoms. In one embodiment of a 5 atom separation, the two oxygen atoms are separated by 4 carbons and one oxygen atom. In a more specific 5 atom separation embodiment, the order of the 5 atoms is -C-C-O-C-C-, whereby a single unit of the functional interacting group (including the two interacting oxygen atoms), is -O- C-C-O-C-C-O-.

Glycol ethers can also be used as solubilizers of neutral or other forms of celecoxib including those that conform with the formula (X):

$$R^1\text{-}O\text{-}((CH_2)_mO)_n\text{-}R^2 \qquad (X)$$

Wherein R^1 and R^2 are independently hydrogen or C_{1-6} alkyl, C_{1-6} alkenyl, phenyl or benzyl groups, but no more than one of R^1 and R^2 is hydrogen; m is an integer of 2 to about 5; and n is an integer of 1 to about 20. It is preferred that one of R^1 and R^2 is a C_{1-4} alkyl group and the other is hydrogen or a C_{1-4} alkyl group; more preferably at least one of R^1 and R^2 is a methyl or ethyl group. It is preferred that m is 2. It is preferred that n is an integer of 1 to about 4, more preferably 2. Non-surfactant glycol ethers, or more specifically glycol ethers of formula (X) and above, can also be specifically excluded from the present invention. Preferably, the glycol ethers are surfactants.

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable co-solvents. Non-limiting examples of co-solvents suitable for use in compositions of the present invention include any glycol ether listed above; alcohols, for example ethanol and n-butanol; glycols not listed above; for example propylene glycol, 1,3-butanediol and polyethylene glycol such as PEG-400; oleic and linoleic acid triglycerides, for example soybean oil; caprylic/capric triglycerides, for example Miglyol™ 812 of Huls; caprylic/capric mono- and diglycerides, for example Capmul™ MCM of Abitec; polyoxyethylene caprylic/capric glycerides such as polyoxyethylene caprylic/capric mono- and diglycerides, for example Labrasol™ of Gattefosse; propylene glycol fatty acid esters, for example propylene glycol laurate; polyoxyethylene castor oil, for example Cremophor™ EL of BASF; polyoxyethylene glyceryl trioleate, for example Tagat™ TO of Goldschmidt; and lower alkyl esters of fatty acids, for example ethyl butyrate, ethyl caprylate and ethyl oleate.

Celecoxib salts are preferred because they are stable, such that they can be formulated as pharmaceutical compositions and stored before administration to a subject. Only after dissolution and subsequent neutralization do the celecoxib salts precipitate as or transform into substantially amorphous neutral and then substantially metastable crystalline neutral forms. Preferably, dissolution and neutralization of celecoxib salts occur *in situ* in the gastrointestinal tract of a subject (e.g., stomach, duodenum, ileum), such that a maximal amount of amorphous and/or metastable crystalline neutral celecoxib is present after administration (e.g., *in vivo*), rather than before administration.

Underivatized valdecoxib refers to valdecoxib that has not been covalently modified, such as by acylating the sulfonamide moiety (e.g., to form a valdecoxib

prodrug). Underivatized valdecoxib can be in the form of either neutral valdecoxib or a salt of valdecoxib.

The present salts and solvates of valdecoxib have several advantages over salts of derivatized valdecoxib (e.g., parecoxib, sodium N-acetyl valdecoxib). First, derivatization of valdecoxib requires an additional synthetic step, requiring the use of additional amounts of organic solvents, which have a high disposal cost. Second, derivatized forms of valdecoxib are typically prodrugs. Prodrugs must be converted, typically *in vivo*, back to the pharmaceutically active form of the drug. As it is desirable for valdecoxib to have a more rapid onset to therapeutic effect, the requirement that a prodrug convert to an active drug potentially delays the therapeutic effect of the drug.

Dissolution Modulation:

In another aspect of the present invention, the dissolution profile of the API is modulated whereby the aqueous dissolution rate or the dissolution rate in simulated gastric fluid or in simulated intestinal fluid, or in a solvent or plurality of solvents is increased. Dissolution rate is the rate at which API solids dissolve in a dissolution medium. For APIs whose absorption rates are faster than the dissolution rates (e.g., steroids), the rate-limiting step in the absorption process is dissolution. Because of a limited residence time at the absorption site, APIs that are not dissolved before they are removed from the intestinal absorption site are considered useless. Therefore, the rate of dissolution has a major impact on the performance of APIs that are poorly soluble. Because of this factor, the dissolution rate of APIs in solid dosage forms is an important, routine, quality control parameter used in the API manufacturing process.

Dissolution rate = $K S (C_s-C)$

where K is the dissolution rate constant, S is the surface area, C_s is the apparent solubility (saturated concentration), and C is the concentration of API in the dissolution media. For rapid API absorption, C_s-C is approximately equal to C_s. The dissolution rate of APIs may be measured by conventional means known in the art.

The increase in the dissolution rate of a composition of the present invention, as compared to the neutral free form, may be specified, such as by 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100%, or by 2, 3, 4, 5 ,6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold greater than the free form

in the same solution. Conditions under which the dissolution rate is measured are discussed above. The increase in dissolution may be further specified by the time the composition remains supersaturated.

Examples of above embodiments include: compositions with a dissolution rate, at 37 degrees C and a pH of 7.0, that is increased at least 5 fold over the neutral free form, compositions with a dissolution rate in SGF that is increased at least 5 fold over the neutral free form, compositions with a dissolution rate in SIF that is increased at least 5 fold over the neutral free form.

The present invention demonstrates that the length of time in which celecoxib, valdecoxib, or other APIs remain in solution can be increased to a surprising high degree by using a salt or co-crystal form with the presence of a precipitation retardant, normally a surfactant (e.g., poloxamer, TPGS, SDS, etc.) and an optional enhancer (e.g., hydroxypropyl cellulose) as discussed herein. The presence of these agents allows the formation of a supersaturated solution of the API and a relatively high concentration of API will remain in solution for an extended period of time (as compared to the neutral free acid). The presence of these components does not preclude the presence of other further agents, including further surfactants such as, polyethylene glycol and polyoxyethylene sorbitan esters. The additional presence of other suitable surfactants is also not precluded and these are listed herein. Further additional agents which might slow the rate of precipitation such as polyvinylpyrrolidone are also not precluded. Neutral free celecoxib, for example, has a solubility in water of less than 1 microgram/mL and cannot be maintained as a supersaturated solution for any appreciable time. The present invention has drawn compositions that can be maintained for a period of time (e.g., 15, 30, 45, 60 minutes and longer) as supersaturated solutions at concentrations 2, 3, 5, 7, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100% greater, or solubilities increased by 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 500, 1000, 10,000, or 100,000 fold over the neutral free form in the same solution (e.g., water or SGF).

The amount of precipitation inhibitor or enhancer may each or together be less than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, or 90 %w/w of the formulated pharmaceutical(. The %w/w for either or both precipitation inhibitor and

enhancer may also be in a range represented by any two integers of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, or 90.

Celecoxib salts of the present invention are typically stable (i.e., more than 90% of the celecoxib salt does not change in composition or crystalline structure) for at least about one week, at least about one month, at least about two months, at least about three months, at least about six months, at least about nine months, at least about one year, or at least about two years at room temperature in the absence of moisture. Room temperature typically ranges from about 15 degrees C to about 30 degrees C. The absence of moisture, as defined herein, refers to celecoxib salts not contacting quantities of liquid, particularly water or alcohols. For purposes of the present invention, gases such as water vapor are not considered to be moisture.

The compositions of the present invention, including the active pharmaceutical ingredient (API) and formulations comprising the API, are suitably stable for pharmaceutical use. Preferably, the API or formulations thereof of the present invention are stable such that when stored at 30 degrees C for 2 years, less than 0.2% of any one degradant is formed. The term degradant refers herein to product(s) of a single type of chemical reaction. For example, if a hydrolysis event occurs that cleaves a molecule into two products, for the purpose of the present invention, it would be considered a single degradant. More preferably, when stored at 40 degrees C for 2 years, less than 0.2% of any one degradant is formed. Alternatively, when stored at 30 degrees C for 3 months, less than 0.2% or 0.15%, or 0.1% of any one degradant is formed, or when stored at 40 degrees C for 3 months, less than 0.2% or 0.15%, or 0.1% of any one degradant is formed. Further alternatively, when stored at 60 degrees C for 4 weeks, less than 0.2% or 0.15%, or 0.1% of any one degradant is formed. The relative humidity (RH) may be specified as ambient (RH), 75% (RH), or as any single integer between 1 to 99% (RH).

Bioavailability Modulation:

The methods of the present invention are used to make a pharmaceutical API formulation with greater solubility, dissolution, bioavailability, AUC, reduced time to T_{max}, the average time from administration to reach peak blood serum levels, higher C_{max}, the average maximum blood serum concentration of API following administration, and longer

$T_{1/2}$, the average terminal half-life of API blood serum concentration following T_{max}, when compared to the neutral free form.

AUC is the area under the curve of plasma concentration of API (not logarithm of the concentration) against time after API administration. The area is conveniently determined by the "trapezoidal rule": The data points are connected by straight line segments, perpendiculars are erected from the abscissa to each data point, and the sum of the areas of the triangles and trapezoids so constructed is computed. When the last measured concentration (C_n, at time t_n) is not zero, the AUC from t_n to infinite time is estimated by C_n/k_{el}.

The AUC is of particular use in estimating bioavailability of APIs, and in estimating total clearance of APIs (Cl_T). Following single intravenous doses, AUC = D/Cl_T, for single compartment systems obeying first-order elimination kinetics Alternatively, AUC = C_0/k_{el}. With routes other than the intravenous, AUC = $F \cdot D/Cl_T$, where F is the absolute bioavailability of the API.

Thus, in a further aspect, the present invention provides a process for modulating the bioavailability of an API when administered in its normal and effective dose range, whereby the AUC is increased, the time to T_{max} is reduced, or C_{max} is increased, which process comprises:

(1) forming a salt or co-crystal of an API;

(2) combining the salt or co-crystal with a precipitation retardant, and optionally, further with an enhancer.

Examples of the above embodiments include: compositions with a time to T_{max} that is reduced by at least 10% as compared to the neutral free form, compositions with a time to T_{max} that is reduced by at least 20% over the free form, compositions with a time to T_{max} that is reduced by at least 40% over the free form, compositions with a time to T_{max} that is reduced by at least 50% over the free form, compositions with a T_{max} that is reduced by at least 60% over the free form, compositions with a T_{max} that is reduced by at least 70% over the free form, compositions with a T_{max} that is reduced by at least 80% over the free form, compositions with a C_{max} that is increased by at least 20% over the free form, compositions with a C_{max} that is increased by at least 30% over the free form, compositions with a C_{max} that is increased by at least 40% over the free form, compositions with a C_{max} that is

increased by at least 50% over the free form, compositions with a C_{max} that is increased by at least 60% over the free form, compositions with a C_{max} that is increased by at least 70% over the free form, compositions with a C_{max} that is increased by at least 80% over the free form, compositions with an AUC that is increased by at least 10% over the free form, compositions with an AUC that is increased by at least 20% over the free form, compositions with an AUC that is increased by at least 30% over the free form, compositions with an AUC that is increased by at least 40% over the free form, compositions with an AUC that is increased by at least 50% over the free form, compositions with an AUC that is increased by at least 60% over the free form, compositions with an AUC that is increased by at least 70% over the free form, or compositions with an AUC that is increased by at least 80% over the free form.

The uptake of a drug by a subject can also be assessed in terms of maximum blood serum concentration and time to reach maximum blood serum concentration. Pharmaceutical compositions with a more rapid onset to therapeutic effect typically reach a higher maximum blood serum concentration (C_{max}) a shorter time after oral administration (T_{max}). Preferably, compositions, preferably including salts, of the present invention have a higher C_{max} and/or a shorter T_{max} than presently-marketed celecoxib. The T_{max} for the compositions of the present invention occurs within about 60 minutes, 55 minutes, 50 minutes, 45 minutes, 40 minutes, 35 minutes, 30 minutes, 25 minutes, 20 minutes, 15 minutes, 10 minutes, or within about 5 minutes of administration (e.g., oral administration). Even more preferably, the therapeutic effects of compositions of the present invention begin to occur within about 60 minutes, 55 minutes, 50 minutes, 45 minutes, 40 minutes, 35 minutes, 30 minutes, within about 25 minutes, within about 20 minutes, within about 15 minutes, within about 10 minutes, or within about 5 minutes of administration (e.g., oral administration). In US Pat. No. 6,579,895, Karim et al. report about a 2.5-fold increase in C_{max} over that of presently-marketed celecoxib (CELEBREX) by the suspension of neutral free form celecoxib particles in an aqueous liquid. The present invention produces an increase in C_{max} of about four-fold over that of the presently-marketed drug. In addition, the present invention yields an increase in the AUC of at least about two-fold over that of presently-marketed celecoxib.

Compositions of the present invention have a bioavailability greater than neutral celecoxib and currently-marketed CELEBREX. In several embodiments, the compositions of the present invention have a bioavailability of at least 50%, 60%, 65%, 70%, 75%, 80%, 85%, 87%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% greater than that of neutral celecoxib and currently-marketed CELEBREX.

Administration of the present invention to a subject may result in effective pain relief. The desired therapeutic effect calls for *inter alia* an appropriate blood serum concentration of the API. Effective blood serum concentrations of celecoxib can range based on many factors (e.g., age, weight, etc.) but generally are about 10 ng/mL to about 500 ng/mL, or about 25 ng/mL to 400 ng/mL, or about 50 ng/mL to about 300 ng/mL. Specifically, about 250 ng/mL is often suitable for effective pain relief. In general, an effective dosage of celecoxib will be found in the range of about 1 mg/kg to about 6 mg/kg body weight. For an average 75 kg subject, this range equates to a celecoxib dose of about 75 mg to about 450 mg. This is particularly in view of the extensive binding of celecoxib to plasma albinum which was known to occur following oral administration (Davies et al., *Clin. Pharmacokinet.* 38:225-242, 2000 and US Pat No. 6,579,895 are herein incorporated as references in their entirety). Thus, one could not have predicted that a particular blood serum concentration would produce analgesia.

An "effective pain-relieving concentration" or "effective pain-relieving blood serum concentration" as used herein is intended to mean a blood serum level in a patient which when tested in a standardized test involving patient scoring of the severity of pain, achieves a mean score indicating pain relief. In one such test as described herein below, patients score pain on a scale of from 0 (no reduction in severity of pain) to 4 (complete relief of pain) and a mean score equal to or greater than a given value is deemed to constitute effective pain-relief. A mean score of 0.5 or greater and, more preferably, 1.0 or greater in such a test, as exemplified herein, is deemed to constitute effective pain relief. The skilled artisan will appreciate, however, that other approaches can be used to assess the severity of pain and relief from such pain.

Thus, one aspect of the present invention involves a therapeutic method for analgesia in which a composition comprising a celecoxib salt or co-crystal, or a valdecoxib salt or co-crystal is administered orally to a subject, in a formulation that provides

detectable pain relief not later than about 30 minutes after oral administration. By "detectable pain relief", it is meant that the formulation produces effective pain relief that is measurable by a standard method such as that described above. For example, a formulation, which achieves a mean score of 0.5 or greater and, more preferably, 1.0 or greater on a scale of from 0 to 4 in a testing system as described above, is deemed to provide detectable pain relief. The invention is not limited to use of any particular type of formulation, so long as it exhibits the pharmacokinetic profile defined herein. Examples of suitable formulation types are described below.

Protocols for conducting human pharmacokinetic studies are well known in the art and any standard protocol can be used to determine whether a particular formulation satisfies the pharmacokinetic criteria set out herein. An example of a suitable protocol is described below.

An advantage of the present invention is that relief of pain, even intense pain as can occur, for example, following oral, general or orthopedic surgery, is achieved significantly faster, i.e., in a significantly shorter time after administration, than is achievable with standard formulations of celecoxib.

Any standard pharmacokinetic protocol can be used to determine blood serum concentration profile in humans following oral administration of a celecoxib formulation, and thereby establish whether that formulation meets the pharmacokinetic criteria set out herein.

Illustratively, a randomized single-dose crossover study can be performed using a group of healthy adult human subjects. The number of subjects is sufficient to provide adequate control of variation in a statistical analysis, and is typically about 10 or greater, although for certain purposes a smaller group can suffice. Each subject receives, by oral administration at time zero, a single dose (e.g., 200 mg) of a test formulation of celecoxib, normally at around 8 am following an overnight fast. The subject continues to fast and remains in an upright position for about 4 hours after administration of the celecoxib formulation. Blood samples are collected from each subject before administration (e.g., 15 minutes prior to administration) and at several intervals after administration. For the present purpose it is preferred to take several samples within the first hour, and to sample less frequently thereafter. Illustratively, blood samples can be collected 15, 30, 45, 60 and

90 minutes after administration, then every hour from 2 to 10 hours after administration. Optionally additional blood samples can be taken later, for example 12 and 24 hours after administration. If the same subjects are to be used for study of a second test formulation, a period of at least 7 days is allowed to elapse before administration of the second formulation. Plasma is separated from the blood samples by centrifugation and the separated plasma is analyzed for celecoxib by a validated high performance liquid chromatography (HPLC) procedure with a lower limit of detection of 10 ng/mL (see for example, Paulson et al., Drug Metab. Dispos. 27:1133-1142, 1999; Paulson et al., Drug Metab. Dispos. 28:308-314, 2000; Davies et al). Blood serum concentrations of celecoxib referenced herein are intended to mean total celecoxib concentrations including both free and bound celecoxib as determined upon extraction from the plasma sample and HPLC detection according to methods known in the art such as those identified above.

Ailments treatable with celecoxib and salts thereof of the present invention are discussed below. Treatment of chronic pain is a preferred embodiment of the present invention.

Dose Response Modulation:

In a further aspect the present invention provides a process for improving the dose response of an API by making a composition of the present invention.

Dose response is the quantitative relationship between the magnitude of response and the dose inducing the response and may be measured by conventional means known in the art. The curve relating effect (dependent variable) to dose (independent variable) for an API-cell system is the "dose-response curve". Typically, the dose-response curve is the measured response to an API plotted against the dose of the API (mg/kg) given. The dose response curve can also be a curve of AUC against the dose of the API given.

The dose-response curve for presently-marketed celecoxib is nonlinear. Preferably, the dose-response curve for celecoxib salt and co-crystal compositions of the present invention is linear or contains a larger linear region than presently-marketed celecoxib. Also, the absorption or uptake of presently-marketed celecoxib depends in part on food effects, such that uptake of celecoxib increases when taken with food, especially fatty food. Preferably, uptake of celecoxib salts of the present invention exhibits a decreased

dependence on food, such that the difference in uptake of celecoxib salts when taken with food and when not taken with food is less than the difference in uptake of presently-marketed celecoxib.

Decreasing Hygroscopicity:

In a still further aspect the present invention provides for APIs with decreased hygroscopicity and a method for decreasing the hygroscopicity of an API by making the same. An aspect of the present invention provides a pharmaceutical composition of an API that is less hygroscopic than amorphous or crystalline free form. Hygroscopicity can be assessed by dynamic vapor sorption analysis, in which 5-50 mg of the compound is suspended from a Cahn microbalance. The compound being analyzed should be placed in a non-hygroscopic pan and its weight should be measured relative to an empty pan composed of identical material and having nearly identical size, shape, and weight. Ideally, platinum pans should be used. The pans should be suspended in a chamber through which a gas, such as air or nitrogen, having a controlled and known percent relative humidity (% RH) is flowed until eqilibrium criteria are met. Typical equilibrium criteria include weight changes of less than 0.01 % change over 3 minutes at constant humidity and temperature. The relative humidity should be measured for samples dried under dry nitrogen to constant weight (<0.01 % change in 3 minutes) at 40 degrees C unless doing so would de-solvate or otherwise convert the material to an amorphous compound. In one aspect, the hygroscopicity of a dried compound can be assessed by increasing the RH from 5 to 95 % in increments of 5 % RH and then decreasing the RH from 95 to 5 % in 5 % increments to generate a moisture sorption isotherm. The sample weight should be allowed to equilibrate between each change in % RH. If the compound deliquesces or becomes amorphous above 75 % RH but below 95 % RH, the experiment should be repeated with a fresh sample and the relative humidity range for the cycling should be narrowed to 5-75 % RH or 10-75 % RH instead of 5-95 % RH. If the sample cannot be dried prior to testing due to lack of form stability, than the sample should be studied using two complete humidity cycles of either 10-75 % RH or 5-95 % RH, and the results of the second cycle should be used if there is significant weight loss at the end of the first cycle.

Hygroscopicity can be defined using various parameters. For purposes of the present invention, a non-hygroscopic molecule should not gain or lose more than 1.0 %, or more preferably, 0.5 % weight at 25 degrees C when cycled between 10 and 75 % RH (relative humidity at 25 degrees C). The non-hygroscopic molecule more preferably should not gain or lose more than 1.0%, or more preferably, 0.5 % weight when cycled between 5 and 95 %RH at 25 degrees C, or 0.25 % of its weight between 10 and 75 % RH. Most preferably, a non-hygroscopic molecule will not gain or lose more than 0.25 % of its weight when cycled between 5 and 95 % RH.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of Callaghan et al., Equilibrium Moisture Content of Pharmaceutical Excipients, in API Dev. Ind. Pharm., Vol. 8, pp. 335-369 (1982). Callaghan et al. classified the degree of hygroscopicity into four classes.

Class 1: Non-hygroscopic	Essentially no moisture increases occur at relative humidities below 90 %.
Class 2: Slightly hygroscopic	Essentially no moisture increases occur at relative humidities below 80 %.
Class 3: Moderately hygroscopic	Moisture content does not increase more than 5 % after storage for 1 week at relative humidities below 60 %.
Class 4: Very hygroscopic	Moisture content increase may occur at relative humidities as low as 40 to 50 %.

Alternatively, for purposes of the present invention, hygroscopicity can be defined using the parameters of the European Pharmacopoeia Technical Guide (1999, p. 86) which has defined hygroscopicity, based on the static method, after storage at 25 degrees C for 24 h at 80 % RH:

Slightly hygroscopic: Increase in mass is less than 2 % m/m and equal to or greater than 0.2 % m/m.

Hygroscopic: Increase in mass is less than 15 % m/m and equal to or greater than 0.2 % m/m.

Very Hygroscopic: Increase in mass is equal to or greater than 15 % m/m.

Deliquescent: Sufficient water is absorbed to form a liquid.

Compositions of the present invention can be set forth as being in Class 1, Class 2, or Class 3, or as being Slightly hygroscopic, Hygroscopic, or Very Hygroscopic. Compositions of the present invention can also be set forth based on their ability to reduce hygroscopicity. Thus, preferred compositions of the present invention are less hygroscopic than the neutral free form. Further included in the present invention are compositions that do not gain or lose more than 1.0 % weight at 25 degrees C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 1.0 % weight under the same conditions. Further included in the present invention are compositions that do not gain or lose more than 0.5 % weight at 25 degrees C when cycled between 10 and 75 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions. Further included in the present invention are compositions that do not gain or lose more than 1.0 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 1.0 % weight under the same conditions. Further included in the present invention are compositions that do not gain or lose more than 0.5% weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions. Further included in the present invention are compositions that do not gain or lose more than 0.25 % weight at 25 degrees C when cycled between 5 and 95 % RH, wherein the reference compound gains or loses more than 0.5 % or more than 1.0 % weight under the same conditions.

Further included in the present invention are compositions that have a hygroscopicity (according to Callaghan et al.) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Included are a Class 1 composition of a Class 2 reference compound, a Class 2 composition of a Class 3 reference compound, a Class 3 composition of a Class 4 reference compound, a Class 1 composition of a Class 3 reference compound, a Class 1 composition of a Class 4 reference compound, or a Class 2 composition of a Class 4 reference compound.

Further included in the present invention are compositions that have a hygroscopicity (according to the European Pharmacopoeia Technical Guide) that is at least one class lower than the reference compound or at least two classes lower than the reference compound. Non-limiting examples include a Slightly hygroscopic composition of a Hygroscopic reference compound, a Hygroscopic composition of a Very Hygroscopic reference compound, a Very Hygroscopic composition of a Deliquescent reference compound, a Slightly hygroscopic composition of a Very Hygroscopic reference compound, a Slightly hygroscopic composition of a Deliquescent reference compound, a Hygroscopic composition of a Deliquescent reference compound.

Celecoxib salts can be characterized by differential scanning calorimetry (DSC). The sodium salt of celecoxib prepared in Example 1 is characterized by at least 3 overlapping endothermic transitions between 50 degrees C and 110 degrees C (Fig. 1). Conditions for DSC can be found in Example 1.

Celecoxib salts can be characterized by thermogravimetric analysis (TGA). The sodium salt product prepared by Example 1 was characterized by TGA, and was determined to have about 3 loosely bound equivalents of water that evaporated between about 30 degrees C and about 40 degrees C, one more tightly bound equivalent of water that evaporated between about 40 degrees C and about 100 degrees C, and one very tightly bound equivalent of water that evaporated between about 140 degrees C and about 160 degrees C (Fig. 2). As described herein however, the sodium salt can exist at different states of hydration depending on the humidity, temperature, and other conditions. Conditions for TGA can be found in the Exemplification section.

Celecoxib salts of the present invention can also be characterized by powder X-ray diffraction (PXRD). The sodium salt of celecoxib prepared by Example 1 had an intense

reflection or peak at a 2-theta angle of 6.36 degrees, and other reflections or peaks at 7.01, 18.72, and 20.83 degrees (Fig. 3). Conditions for PXRD can be found in Example 1.

Celecoxib salts may comprise solvate molecules and can occur in a variety of solvation states, also known as solvates. Thus, celecoxib salts can exist as crystalline polymorphs. Polymorphs are different crystalline forms of the same drug substance, and in the present use of the term include solvates and hydrates. For example, different polymorphs of a celecoxib salt can be obtained by varying the method of preparation (compare Examples). Crystalline polymorphs typically have different solubilities, such that a more thermodynamically stable polymorph is less soluble than a less thermodynamically stable polymorph. Pharmaceutical polymorphs can also differ in properties such as shelf-life, bioavailability, morphology, vapor pressure, density, color, and compressibility.

Suitable solvate molecules include water, alcohols, other polar organic solvents, and combinations thereof. Alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, propylene glycol and t-butanol. Propylene glycol solvates are particularly preferred because they are more stable and less hygroscopic than other forms. Alcohols also include polymerized alcohols such as polyalkylene glycols (e.g., polyethylene glycol, polypropylene glycol). In an embodiment, water is the solvent. In embodiments of the invention, a celecoxib salt contains about 0.0 %, less than 0.5 %, 0.5, less than 1.0 %, 1.0, less than 1.5 %, 1.5, less than 2.0 %, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5 or about 6.0 equivalents, or about 1.0 to about 6.0, 2.0 to about 5.0, 3.0 to about 6.0, 3.0 to about 5.0, 1.0 to about 4.0, 2.0 to about 4.0, 1.0 to about 3.0, 2.0 to about 3.0, 0.0 to about 3.0, 0.5 to about 3.0, 0.0 to about 2.0, 0.5 to about 2.0, 0.0 to about 1.5, 0.5 to about 1.5, 1.0 to about 1.5, or 0.5 to about 1.0 equivalents of water per equivalent of salt. The amount of water equivalents in the above hydrates is primarily affected by the experimental conditions (e.g., temperature). Solvate molecules can be removed from a crystalline salt, such that the salt is either a partial or complete desolvate. If the solvate molecule is water (forming a hydrate), then a desolvated salt is said to be a dehydrate. A salt with all water removed is anhydrous. Solvate molecules can be removed from a salt by methods such as heating, treating under vacuum or reduced pressure, blowing dry air over a salt, or a combination thereof. Following desolvation, there are typically about one

to about five equivalents, about one to about four equivalents, about one to about three equivalents, or about one to about two equivalents of solvent per equivalent of salt in a crystal.

Pharmaceuticals including celecoxib, can co-crystallize with one or more other substances. The term "co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point and heats of fusion. Solvates of API compounds that do not further comprise a co-crystal forming compound are not co-crystals according to the present invention. The co-crystals may however, include one or more solvent molecules in the crystalline lattice. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention, but crystalline material comprised of only one solid and one or more liquids (at room temperature) are not included by the term "co-crystal". The co-crystals may include a co-crystal former and a salt of an API, but the API and the co-crystal former of the present invention are constructed or bonded together through hydrogen bonds. Other modes of molecular recognition may also be present including, Π-stacking, guest-host complexation and van der Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other. An alternative embodiment provides for a co-crystal wherein the co-crystal former is a second API. In another embodiment, the co-crystal former is not an API.

In several embodiments of the present invention, the composition is a co-crystal. In other embodiments the co-crystal formers are selected from one or two (for ternary co-crystals) of the following: saccharin, nicotinamide, pyridoxine (4-pyridoxic acid), acesulfame, glycine, arginine, asparagine, cysteine, glutamine, histidine, isoleucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine, aspartic acid, glutamic acid, tryptophan, adenine, acetohydroxamic acid, alanine, allopurinaol, 4-aminobenzoic acid, cyclamic acid, 4-ethoxyphenyl urea, 4-aminopyridine, leucine, nicotinic acid, serine, tris, vitamin k5, xylito, succinic acid, tartaric acid, pyridoxamine, ascorbic acid, hydroquinone, salicylic acid, benzoic acid, caffeine, benzenesulfonic acid, 4-chlorobenzene-sulfonic acid,

citric acid, fumaric acid, gluconic acid, glutaric acid, glycolic acid, hippuric acid, maleic acid, malic acid, mandelic acid, malonic acid, 1,5-napthalene-disulfonic acid (armstrong's acid), clemizole, imidazole, glucosamine, piperazine, procaine, or urea.

Celecoxib salts may be prepared by contacting celecoxib with a solvent. Suitable solvents include water, alcohols, other polar organic solvents, and combinations thereof. Water and isopropanol are preferred solvents. Celecoxib is reacted with a base, where suitable bases are listed above, such that celecoxib forms a salt and preferably dissolves. Bases can be added to celecoxib with the solvent (i.e., dissolved in the solvent), such that celecoxib is solvated and deprotonated essentially simultaneously, or bases can be added after the celecoxib has been contacted with solvent (e.g., see Examples). In the latter scenario, bases can either be dissolved in a solvent, which can be either the solvent already contacting celecoxib or a different solvent, can be added as a neat solid or liquid, or a combination thereof. Sodium hydroxide and sodium ethoxide are preferred bases. The amount of base required is discussed above. The solvent can be evaporated to obtain crystals of the celecoxib salt, or the celecoxib salt may precipitate and/or crystallize independent of evaporation. Crystals of a celecoxib salt can be filtered to remove bulk solvent. Methods of removing solvated solvent molecules are discussed above.

Excipients employed in pharmaceutical compositions of the present invention can be solids, semi-solids, liquids or combinations thereof. Preferably, excipients are solids. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with a drug or therapeutic agent. A pharmaceutical composition of the invention contains a desired amount of celecoxib per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a dispersion, a liquid, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for example, of a suspension or transdermal patch. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the drug, such as tablets or capsules.

Non-limiting examples of excipients that can be used to prepare pharmaceutical compositions of the invention follow.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable carriers or diluents as excipients. Suitable carriers or diluents illustratively include, but are not limited to, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and hydrolyzed starches (e.g., Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (e.g., Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of alpha- and amorphous cellulose (e.g., RexcelJ), powdered cellulose, and hydroxypropylmethylcellulose (HPMC); calcium carbonate; glycine; bentonite; block co-polymers; polyvinylpyrrolidone; and the like. Such carriers or diluents, if present, constitute in total about 5 % to about 99 %, preferably about 10 % to about 85 %, and more preferably about 20 % to about 80 %, of the total weight of the composition. The carrier, carriers, diluent, or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose, mannitol, dibasic sodium phosphate, and microcrystalline cellulose (particularly Avicel™ PH (of FMC) microcrystalline cellulose such as Avicel™ PH 101), either individually or in combination, are preferred diluents. These diluents are chemically compatible with celecoxib. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a granulated composition) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of celecoxib, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties and tablet properties.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet

formulations. Suitable disintegrants include, but are not limited to, either individually or in combination, starches, including sodium starch glycolate (e.g., Explotab™ of PenWest) and pregelatinized corn starches (e.g., National™ 1551 of National Starch and Chemical Company, National™ 1550, and Colocorn™ 1500), clays (e.g., Veegum™ HV of R.T. Vanderbilt), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (e.g., Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2 % to about 30 %, preferably about 0.2 % to about 10 %, and more preferably about 0.2 % to about 5 %, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2 % to about 10 %, more preferably about 0.2 % to about 7 %, and still more preferably about 0.2 % to about 5 %, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated pharmaceutical compositions of the present invention.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Such binding agents may also further prevent or inhibit crystallization or recrystallization/precipitation of a celecoxib salt of the present invention once the salt has been dissolved in a solution. Suitable binding agents and adhesives include, but are not limited to, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (e.g., National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (e.g., Tylose™); alginic acid and salts of

alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (e.g., Klucel™ of Aqualon); and ethylcellulose (e.g., Ethocel™ of the Dow Chemical Company). Such binding agents and/or adhesives, if present, constitute in total about 0.5 % to about 25 %, preferably about 0.75 % to about 15 %, and more preferably about 1 % to about 10 %, of the total weight of the pharmaceutical composition.

Many of the binding agents are polymers comprising amide, ester, ether, alcohol or ketone groups and, as such, are preferably included in pharmaceutical compositions of the present invention. Polyvinylpyrrolidones such as povidone K-30 are especially preferred. Polymeric binding agents can have varying molecular weight, degrees of crosslinking, and grades of polymer. Polymeric binding agents can also be copolymers, such as block co-polymers that contain mixtures of ethylene oxide and propylene oxide units. Variation in these units' ratios in a given polymer affects properties and performance. Examples of block co-polymers with varying compositions of block units are Poloxamer 188 and Poloxamer 237 (BASF Corporation).

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the celecoxib in close association with water, a condition that is believed to improve bioavailability of the composition. Such wetting agents can also be useful in solubilizing or increasing the solubility of metal salts of celecoxib.

Non-limiting examples of surfactants that can be used as wetting agents (not necessarily as the precipitation retardant) in pharmaceutical compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (e.g., Labrasol™ of Gattefosse), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid

esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (e.g., Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (e.g., Lauroglycol™ of Gattefosse), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25 % to about 15 %, preferably about 0.4 % to about 10 %, and more preferably about 0.5 % to about 5 %, of the total weight of the pharmaceutical composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25 % to about 7 %, more preferably about 0.4 % to about 4 %, and still more preferably about 0.5 % to about 2 %, of the total weight of the pharmaceutical composition.

Pharmaceutical compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, but are not limited to, either individually or in combination, glyceryl behapate (e.g., Compritol™ 888 of Gattefosse); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (e.g., Sterotex™ of Abitec); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (e.g., Carbowax™ 4000 and Carbowax™ 6000 of the Dow Chemical Company); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0. 1 % to about 10 %, preferably about 0.2 % to about 8 %, and more preferably about 0.25 % to about 5 %, of the total weight of the pharmaceutical composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include, but are not limited to, talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1 % to about 10 %, more preferably

about 0.25 % to about 5 %, and still more preferably about 0.5 % to about 2 %, of the total weight of the pharmaceutical composition.

Glidants can be used to promote powder flow of a solid formulation. Suitable glidants include, but are not limited to, colloidal silicon dioxide, starch, talc, tribasic calcium phosphate, powdered cellulose and magnesium trisilicate. Colloidal silicon dioxide is particularly preferred. Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical arts and can be used in pharmaceutical compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of pharmaceutical compositions of the invention. When present in pharmaceutical compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30 % to about 75 %, and preferably about 45 % to about 70 %, for example about 60 %, by weight of the pharmaceutical composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to promote disintegration of the dosage form, provides improved dispersion of the celecoxib in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of celecoxib from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, an effervescent agent is preferably present in an amount of about 1 % to about 20 %, more preferably about 2.5 % to about 15 %, and still more preferably about 5 % to about 10 % by weight of the pharmaceutical composition.

An "effervescent agent" herein is an agent comprising one or more compounds which, acting together or individually, evolve a gas on contact with water. The gas evolved is generally oxygen or, most commonly, carbon dioxide. Preferred effervescent agents comprise an acid and a base that react in the presence of water to generate carbon

dioxide gas. Preferably, the base comprises an alkali metal or alkaline earth metal carbonate or bicarbonate and the acid comprises an aliphatic carboxylic acid.

Non-limiting examples of suitable bases as components of effervescent agents useful in the invention include carbonate salts (e.g., calcium carbonate), bicarbonate salts (e.g., sodium bicarbonate), sesquicarbonate salts, and mixtures thereof. Calcium carbonate is a preferred base.

Non-limiting examples of suitable acids as components of effervescent agents and/or solid organic acids useful in the invention include citric acid, tartaric acid (as D-, L-, or D/L-tartaric acid), malic acid, maleic acid, fumaric acid, adipic acid, succinic acid, acid anhydrides of such acids, acid salts of such acids, and mixtures thereof. Citric acid is a preferred acid.

In a preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the weight ratio of the acid to the base is about 1:100 to about 100:1, more preferably about 1:50 to about 50:1, and still more preferably about 1:10 to about 10:1. In a further preferred embodiment of the invention, where the effervescent agent comprises an acid and a base, the ratio of the acid to the base is approximately stoichiometric.

Excipients which solubilize metal salts of celecoxib typically have both hydrophilic and hydrophobic regions, or are preferably amphiphilic or have amphiphilic regions. One type of amphiphilic or partially-amphiphilic excipient comprises an amphiphilic polymer or is an amphiphilic polymer. A specific amphiphilic polymer is a polyalkylene glycol, which is commonly comprised of ethylene glycol and/or propylene glycol subunits. Such polyalkylene glycols can be esterified at their termini by a carboxylic acid, ester, acid anhyride or other suitable moiety. Examples of such excipients include poloxamers (symmetric block copolymers of ethylene glycol and propylene glycol; e.g., poloxamer 237), polyalkyene glycolated esters of tocopherol (including esters formed from a di- or multi-functional carboxylic acid; e.g., d-alpha-tocopherol polyethylene glycol-1000 succinate), and macrogolglycerides (formed by alcoholysis of an oil and esterification of a polyalkylene glycol to produce a mixture of mono-, di- and tri-glycerides and mono- and di-esters; e.g., stearoyl macrogol-32 glycerides). Such pharmaceutical compositions are advantageously administered orally.

Pharmaceutical compositions of the present invention can comprise about 10 % to about 50 %, about 25 % to about 50 %, about 30 % to about 45 %, or about 30 % to about 35 % by weight of a metal salt of celecoxib; about 10 % to about 50 %, about 25 % to about 50 %, about 30 % to about 45 %, or about 30 % to about 35 % by weight of an excipient which inhibits precipitation; and about 5 % to about 50 %, about 10 % to about 40 %, about 15 % to about 35 %, or about 30 % to about 35 % by weight of a binding agent. In one example, the weight ratio of the metal salt of celecoxib to the excipient which inhibits precipitation to binding agent is about 1 to 1 to 1.

The resulting formulations described above are both physically and chemically stable. The present invention can be prepared in solid dosage form well in advance (e.g., months) of oral administration without the risk of premature neutralization or precipitation of the API. Liquid suspensions of celecoxib particles can suffer from a tendency of the particles to agglomerate and/or increase in size by crystal growth after only several minutes of standing. This crystal growth can significantly reduce the bioavailability and therapeutic effect of the drug.

Solid dosage forms of the invention can be prepared by any suitable process, and are not limited to processes described herein. An illustrative process comprises (i) a step of blending a celecoxib salt of the invention with one or more excipients to form a blend, and (ii) a step of tableting or encapsulating the blend to form tablets or capsules, respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending the celecoxib salt to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art. A celecoxib salt is advantageously granulated to form particles of about 10 micrometer to about 1000 micrometer, about 25 micrometer to about 500 micrometer, or about 50 micrometer to about 300 micrometer. More specifically, particles of about 100 micrometers in diameter are well suited to yield the desired therapeutic effect. One or more diluents, one or more disintegrants and one or more binding agents may be added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants may be added after

granulating but before tableting or encapsulating. A lubricant may be added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in drug content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein a celecoxib salt is suspended with one or more excipients in one or more sprayable liquids, preferably a non-protic (e.g., non-aqueous or non-alcoholic) sprayable liquid, and then is rapidly spray dried over a current of warm air.

A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable.

Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Celecoxib dosage forms of the invention preferably comprise celecoxib in a daily dosage amount of about 10 mg to about 1000 mg, more preferably about 50 mg to about 100 mg, about 100 mg to about 150 mg, 150 mg to about 200 mg, 200 mg to about 250 mg, 250 mg to about 300 mg, 300 mg to about 350 mg, 350 mg to about 400 mg, 400 mg to about 450 mg 450 mg to about 500 mg, 500 mg to about 550 mg, 550 mg to about 600 mg, 600 mg to about 700 mg, and 700 mg to about 800 mg.

Pharmaceutical compositions of the invention comprise one or more orally deliverable dose units. Each dose unit comprises celecoxib in a therapeutically effective amount that is preferably those listed. The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic or prophylactic agent, in the present case celecoxib, suitable for a single oral administration to provide a therapeutic effect. Typically one dose unit, or a small plurality (up to about 4) of dose

units, in a single administration provides a dose comprising a sufficient amount of the agent to result in the desired effect. Administration of such doses can be repeated as required, typically at a dosage frequency of 1, 2, 3, or 4 times per day.

It will be understood that a therapeutically effective amount of celecoxib for a subject is dependent *inter alia* on the body weight of the subject. A "subject" to which a celecoxib salt or a pharmaceutical composition thereof can be administered includes a human subject of either sex and of any age, and also includes any nonhuman animal, particularly a warm-blooded animal, more particularly a domestic or companion animal, illustratively a cat, dog or horse. When the subject is a child or a small animal (e.g., a dog), for example, an amount of celecoxib (measured as the neutral form of celecoxib, that is, not including counterions in a salt or water in a hydrate) relatively low in the preferred range of about 10 mg to about 1000 mg is likely to provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (e.g., a horse), achievement of such blood serum concentrations of celecoxib is likely to require dose units containing a relatively greater amount of celecoxib.

Typical dose units in a pharmaceutical composition of the invention contain about 10, 20, 25, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 mg of celecoxib. For an adult human, a therapeutically effective amount of celecoxib per dose unit in a composition of the present invention is typically about 50 mg to about 400 mg. Especially preferred amounts of celecoxib per dose unit are about 100 mg to about 200 mg, for example about 100 mg or about 200 mg. Other doses that are not in current use for CELEBREX may become preferred, if the bioavailability is changed with a novel formulation. For instance, 300 mg may become a preferred dose for certain indications.

A dose unit containing a particular amount of celecoxib can be selected to accommodate any desired frequency of administration used to achieve a desired daily dosage. The daily dosage and frequency of administration, and therefore the selection of appropriate dose unit, depends on a variety of factors, including the age, weight, sex and medical condition of the subject, and the nature and severity of the condition or disorder, and thus may vary widely.

For pain management, pharmaceutical compositions of the present invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably

about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a pharmaceutical composition of the invention. The daily dose can be administered in one to about four doses per day. Administration at a rate of one 50 mg dose unit four times a day, one 100 mg dose unit or two 50 mg dose units twice a day, or one 200 mg dose unit, two 100 mg dose units or four 50 mg dose units once a day is preferred.

The term "oral administration" herein includes any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is immediately swallowed, although each are embodiments of the invention. Thus, "oral administration" includes buccal and sublingual as well as esophageal administration. Absorption of the agent can occur in any part or parts of the gastrointestinal tract including the mouth, esophagus, stomach, duodenum, ileum and colon. The term "orally deliverable" herein means suitable for oral administration. Pharmaceutically acceptable salts of celecoxib and valdecoxib can be administered by controlled- or delayed-release means. Controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled release counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; 4) usage of less total drug; 5) reduction in local or systemic side effects; 6) minimization of drug accumulation; 7) reduction in blood level fluctuations; 8) improvement in efficacy of treatment; 9) reduction of potentiation or loss of drug activity; and 10) improvement in speed of control of diseases or conditions. Kim, Cherng-ju, Controlled Release Dosage Form Design, 2 (Technomic Publishing, Lancaster, Pa.: 2000).

Conventional dosage forms generally provide rapid or immediate drug release from the formulation. Depending on the pharmacology and pharmacokinetics of the drug, use of conventional dosage forms can lead to wide fluctuations in the concentrations of the drug in a patient's blood and other tissues. These fluctuations can impact a number of parameters, such as dose frequency, onset of action, duration of efficacy, maintenance of therapeutic blood levels, toxicity, side effects, and the like. Advantageously, controlled-release formulations can be used to control a drug's onset of action, duration of action, plasma levels within the therapeutic window, and peak blood levels. In particular, controlled- or extended-release dosage forms or formulations can be used to ensure that the maximum effectiveness of a drug is achieved while minimizing potential adverse effects and safety concerns, which can occur both from under dosing a drug (i.e., going below the minimum therapeutic levels) as well as exceeding the toxicity level for the drug.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, ionic strength, osmotic pressure, temperature, enzymes, water, and other physiological conditions or compounds.

A variety of known controlled- or extended-release dosage forms, formulations, and devices can be adapted for use with the celecoxib and valdecoxib salts and compositions of the invention. Examples include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,733,566; and 6,365,185 B1; each of which is incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems (such as OROS® (Alza Corporation, Mountain View, Calif. USA)), multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to

provide the desired release profile in varying proportions. Additionally, ion exchange materials can be used to prepare immobilized, adsorbed salt forms of celecoxib and valdecoxib and thus effect controlled delivery of the drug. Examples of specific anion exchangers include, but are not limited to, Duolite® A568 and Duolite® AP143 (Rohm & Haas, Spring House, PA. USA).

One embodiment of the invention encompasses a unit dosage form which comprises a pharmaceutically acceptable salt of celecoxib or valdecoxib (e.g., a sodium, potassium, or lithium salt), or a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof, and one or more pharmaceutically acceptable excipients or diluents, wherein the pharmaceutical composition or dosage form is formulated for controlled-release. Specific dosage forms utilize an osmotic drug delivery system.

A particular and well-known osmotic drug delivery system is referred to as OROS® (Alza Corporation, Mountain View, Calif. USA). This technology can readily be adapted for the delivery of compounds and compositions of the invention. Various aspects of the technology are disclosed in U.S. Pat. Nos. 6,375,978 B1; 6,368,626 B1; 6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420; each of which is incorporated herein by reference. Specific adaptations of OROS® that can be used to administer compounds and compositions of the invention include, but are not limited to, the OROS® Push-Pull™, Delayed Push-Pull™, Multi-Layer Push-Pull™, and Push-Stick™ Systems, all of which are well known. See, e.g., http://www.alza.com. Additional OROS® systems that can be used for the controlled oral delivery of compounds and compositions of the invention include OROS®-CT and L-OROS®. Id.; see also, Delivery Times, vol. II, issue II (Alza Corporation).

Conventional OROS® oral dosage forms are made by compressing a drug powder (e.g., celecoxib or valdecoxib salt) into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating (e.g., with a laser). Kim, Cherng-ju, Controlled Release Dosage Form Design, 231-238 (Technomic Publishing, Lancaster, Pa.: 2000). The advantage of such dosage forms is that the delivery rate of the drug is not influenced by physiological or experimental conditions. Even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium. But because these advantages are provided by a build-up

of osmotic pressure within the dosage form after administration, conventional OROS® drug delivery systems cannot be used to effectively deliver drugs with low water solubility. Id. at 234. Because celecoxib and valdecoxib salts and complexes of this invention (e.g., celecoxib sodium) are far more soluble in water than celecoxib or valdecoxib itself, they are well suited for osmotic-based delivery to patients. This invention does, however, encompass the incorporation of celecoxib, valdecoxib, and non-salt isomers and isomeric mixtures thereof, into OROS® dosage forms.

A specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry or substantially dry state drug layer located within the cavity adjacent to the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow-promoting layer interposed between the inner surface of the wall and at least the external surface of the drug layer located within the cavity, wherein the drug layer comprises a salt of celecoxib, valdecoxib, or a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,368,626, the entirety of which is incorporated herein by reference.

Another specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; the drug layer comprising a liquid, active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the liquid, active agent formulation, the dosage form optionally having a placebo layer between the exit orifice and the drug layer, wherein the active agent formulation comprises a salt of celecoxib, valdecoxib, or a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,342,249, the entirety of which is incorporated herein by reference.

In a particular embodiment of the present invention, multiple pellets can be incorporated into the formulation, each with a distinct coating thickness. This will allow each pellet to dissolve at an exclusive, predetermined time interval following administration. The result is an increased duration of the desired therapeutic effect. Such a controlled-release (CR) formulation can reduce the frequency at which a pharmaceutical must be administered to a patient, thereby decreasing the total amount of drug intake. Improvements such as reduced side effects, reduced drug accumulation, and reduced fluctuations in blood serum level are advantages of controlled-release formulations. A further embodiment allows the formulation to include more than one therapeutic agent. Pellets of two or more APIs can be incorporated, each with distinct coating thicknesses, thereby resulting in binary, tertiary, or higher order pharmaceuticals. (Kim, Cherng-ju, Controlled Release Dosage Form Design, Technomic Publishing, Lancaster, PA 2000).

An important aspect of the administration of drugs in conventional forms is the fluctuation between high and low blood serum concentration of the drug in the period between the administration of two successive doses. In fact, if the drug is too rapidly absorbed, excessive plasma levels may be attained, leading to undesirable and even toxic side effects. On the other hand, drugs possessing a short half-life are eliminated too rapidly and require therefore frequent administrations. In both cases the patient must be careful because particular attention and constancy in the administration is required during therapy and such conditions cannot always be easily obtained. Many efforts have been made to formulate pharmaceutical preparations able to protract in time the activity of the drug in the body at optimum plasma levels, reducing the number of administrations and thus improving the response of the patient to the treatment.

The preparation of pharmaceutical compositions intended to supply a gradual and controlled release in time of the active ingredient is well known in the pharmaceutical technology field. Systems are known comprising tablets, capsules, microcapsules, microspheres and formulations in general, in which the active ingredient is released gradually by various means including the following. Particles containing the API can be coated with individual specific external coatings so that the release of active medicament from the inner core is separated by sequential intervals. The number of defined pulses of drug released by a formulation can range from about 1 to about 10, or more specifically

from about 1 to about 5. When applicable, a drug-free lag time can be instituted before the release of first dosage of the active medicament. This drug-free lag time is accomplished by delaying the first pulse-release.

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the API in desired areas of the gastro-intestinal (GI) tract, e.g., the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions which release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the API is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described in detail in U.S. Pat. Nos. 5,273,760 and 5,286,493, and are hereby incorporated by reference in their entirety. Other examples of sustained release formulations and coatings which may

be used in accordance with the present invention include U.S. Pat. Nos. 5,324,351, 5,356,467, and 5,472,712, also hereby incorporated by reference in their entirety.

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

One commercially-available aqueous dispersion of ethylcellulose is Aquacoat® (FMC Corp., Philadelphia, Pa., U.S.A.). Aquacoat® is prepared by dissolving the ethylcellulose in a water-immiscible organic solvent and then emulsifying the same in water in the presence of a surfactant and a stabilizer. After homogenization to generate submicron droplets, the organic solvent is evaporated under vacuum to form a pseudolatex. The plasticizer is not incorporated in the pseudolatex during the manufacturing phase. Thus, prior to using the same as a coating, it is necessary to intimately mix the Aquacoat® with a suitable plasticizer prior to use.

Another aqueous dispersion of ethylcellulose is commercially available as Surelease® (Colorcon, Inc., West Point, Pa., U.S.A.). This product is prepared by incorporating plasticizer into the dispersion during the manufacturing process. A hot melt of a polymer, plasticizer (dibutyl sebacate), and stabilizer (oleic acid) is prepared as a homogeneous mixture, which is then diluted with an alkaline solution to obtain an aqueous dispersion which can be applied directly onto substrates.

In other preferred embodiments of the present invention, the hydrophobic material comprising the controlled release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate co-polymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers arc well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit® from Rohm Tech, Inc. There are several different types of Eudragit®. For example, Eudragit® E is an example of a methacrylic acid copolymer which swells and dissolves in acidic media. Eudragit® L is a methacrylic acid copolymer which does not swell at about pH <5.7 and is soluble at about pH >6. Eudragit® S does not swell at about pH <6.5 and is soluble at about pH >7. Eudragit® RL and Eudragit® RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit® RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit® RL30D and Eudragit® RS30D, respectively. Eudragit® RL30D and Eudragit® RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL30D and 1:40 in Eudragit® RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit® RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit® RL, 50% Eudragit® RL and 50% Eudragit® RS, and 10% Eudragit® RL:Eudragit® 90% RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit® L.

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticizer in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethylcellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticizer into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1 to about 50 percent by weight of the film-former. Concentration of the plasticizer, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticizers for ethylcellulose include water insoluble plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticizers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticizers which have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit® RL/RS lacquer solutions include polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticizer for the aqueous dispersions of ethyl cellulose of the present invention.

It has further been found that the addition of a small amount of talc reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing agent.

When a hydrophobic material is used to coat inert pharmaceutical beads, a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

The controlled release bead formulations of the present invention slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which the plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with a therapeutically active agent are prepared, e.g., by dissolving the therapeutically active agent in water and then spraying the solution onto a substrate, for example, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the API to the beads, and/or to color the solution, etc. For example, a product which includes hydroxypropylmethylcellulose, etc. with or without colorant (e.g., Opadry®, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in this example beads, may then be optionally overcoated with a barrier agent, to separate the therapeutically active agent from the hydrophobic controlled release coating. An example of a suitable barrier agent is one which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an

effective amount of plasticizer, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat® or Surelease®, may be used. If Surelease® is used, it is not necessary to separately add a plasticizer. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit® can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticizer, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Color may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, color may be added to Aquacoat® via the use of alcohol or propylene glycol based color dispersions, milled aluminum lakes and opacifiers such as titanium dioxide by adding color with shear to water soluble polymer solution and then using low shear to the plasticized Aquacoat®. Alternatively, any suitable method of providing color to the formulations of the present invention may be used. Suitable ingredients for providing color to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and color pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

Plasticized hydrophobic material may be applied onto the substrate comprising the therapeutically active agent by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidized-bed system is used in which an air jet, injected from underneath, fluidizes the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined controlled release of said therapeutically active agent when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, is preferably applied, taking into account the physical characteristics of the therapeutically active agent, the manner of incorporation of the plasticizer, etc. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry®, is optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the therapeutically active agent from the controlled release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble

material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Pat. Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864 (all of which are hereby incorporated by reference). The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

The present invention may include dual-release compositions whereby a celecoxib salt is formulated so as to contain both a fast acting component and a sustained release component of drug delivery. This formulation allows for both relatively fast and prolonged therapeutic effects while minimizing administration frequency. Dual-release compositions are further described in WO 01/45706 A1, the contents of which are herein incorporated by reference in their entirety.

Celecoxib compositions useful in methods of the present invention can be used in combination therapies with opioids and other analgesics. The compound to be administered in combination with a celecoxib composition useful in methods of the invention can be formulated separately from said composition or co-formulated with said

composition. Where a celecoxib composition is co-formulated with a second drug, for example an opioid drug, the second drug can be formulated in immediate-release, rapid-onset, sustained-release or dual-release form. In a specific embodiment of the present invention, celecoxib can be combined with an anti-platelet drug for example, but not limited to, tirofiban, aspirin, dipyridamole, anagrelide, epoprostenol, eptifibatide, clopidogrel, cilostazol, abciximab, or ticlopidine.

Pharmaceutical compositions of the invention are useful in treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such pharmaceutical compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional non-steroidal anti-inflammatory drugs (NSAIDs) that lack selectivity for COX-2 over COX-1. In particular, pharmaceutical compositions of the invention have reduced the potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, reduced effect on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in subjects with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems, kidney disease, or in subjects prior to surgery or subjects taking anticoagulants.

Contemplated pharmaceutical compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

Such pharmaceutical compositions are useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendonitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including

hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

Pharmaceutical compositions of the present invention are useful to treat gastrointestinal conditions such as, but not limited to, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

Such pharmaceutical compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

In addition, these pharmaceutical compositions are useful in treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

Also, such pharmaceutical compositions are useful in treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis.

The pharmaceutical compositions are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

Such pharmaceutical compositions are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

Further, pharmaceutical compositions of the present invention are useful in treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. For example, such compositions are useful for relief of pain, fever and inflammation in a variety of conditions including rheumatic fever,

influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, bums, and trauma following surgical and dental procedures.

The present invention is further directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method comprising oral administration of a pharmaceutical composition of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above. The present pharmaceutical compositions can be used in combination with other therapies or therapeutic agents, including but not limited to, therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, GABA active agents, norexin neuropeptide modulators, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, alpha-bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen,

butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, modafinil, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsahnide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid,

ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, topiramate, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition, Therapeutic Category and Biological Activity Index, ed. S. Budavari (1996), pp. Ther-2 to Ther-3 and Ther-12 (Analgesic (D)ental), Analgesic (Narcotic), Analgesic (Non-narcotic), Anti-inflammatory (Non-steroidal)).

Pharmaceutical compositions of the present invention are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

These pharmaceutical compositions are also useful in treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such pharmaceutical compositions are useful in treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

Moreover, pharmaceutical compositions of the present invention are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer,

such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such pharmaceutical compositions can also be used to treat fibrosis that occurs with radiation therapy. These pharmaceutical compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, pharmaceutical compositions of the present invention can be used to prevent polyps from forming in subjects at risk of FAP.

Also, the pharmaceutical compositions inhibit prostanoid-induced smooth muscle contraction by inhibiting synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (i.e., treatment of osteoporosis), and for treatment of glaucoma.

Preferred uses for pharmaceutical compositions of the invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for treatment of Alzheimer's disease, and for colon cancer chemoprevention. A particular preferred use is for rapid pain management, such as when a celecoxib salt or a pharmaceutical composition thereof is effective in treating pain within about 30 minutes or less.

Besides being useful for human treatment, pharmaceutical compositions of the invention are useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals. More particularly, pharmaceutical

compositions of the invention are useful for treatment of COX-2 mediated disorders in horses, dogs, and cats.

EXEMPLIFICATION

Below are standard procedures for acquiring Raman, PXRD, DSC and TGA data herein. These procedures will be followed for each respective method of analysis herein unless otherwise indicated.

Procedure for Raman Acquisition, Filtering and Binning

Acquisition

The sample was either left in the glass vial in which it was processed or an aliquot of the sample was transferred to a glass slide. The glass vial or slide was positioned in the sample chamber. The measurement was made using an Almega™ Dispersive Raman (Almega™ Dispersive Raman, Thermo-Nicolet, 5225 Verona Road, Madison, WI 53711-4495) system fitted with a 785 nm laser source. The sample was manually brought into focus using the microscope portion of the apparatus with a 10x power objective (unless otherwise noted), thus directing the laser onto the surface of the sample. The spectrum was acquired using the parameters outlined in Table 1. (Exposure times and number of exposures may vary; changes to parameters will be indicated for each acquisition.)

Filtering and Binning

Each spectrum in a set was filtered using a matched filter of feature size 25 to remove background signals, including glass contributions and sample fluorescence. This is particularly important as large background signal or fluorescence limit the ability to accurately pick and assign peak positions in the subsequent steps of the binning process. Filtered spectra were binned using the peak pick and bin algorithm with the parameters given in Table 2. The sorted cluster diagrams for each sample set and the corresponding cluster assignments for each spectral file were used to identify groups of samples with similar spectra, which was used to identify samples for secondary analyses.

Table 1. Raman Spectral acquisition parameters

Parameter	Setting Used
Exposure time (s)	2.0
Number of exposures	10
Laser source wavelength (nm)	785
Laser power (%)	100
Aperture shape	pin hole
Aperture size (um)	100
Spectral range (cm^{-1})	104-3428
Grating position	Single
Temperature at acquisition (degrees C)	24.0

Table 2. Raman Filtering and Binning Parameters

Parameter	Setting Used
Filtering Parameters	
Filter type	Matched
Filter size	25
QC Parameters	
Peak Height Threshold	1000
Region for noise test (cm^{-1})	0-10000
RMS noise threshold	10000
Automatically eliminate failed spectra	Yes
Region of Interest	
Include (cm^{-1})	104-3428
Exclude region I (cm^{-1})	
Exclude region II (cm^{-1})	
Exclude region III (cm^{-1})	
Exclude region IV (cm^{-1})	
Peak Pick Parameters	
Peak Pick Sensitivity	Variable
Peak Pick Threshold	100
Peak Comparison Parameters	
Peak Window (cm^{-1})	2
Analysis Parameters	
Number of clusters	Variable

Any one or combination of two, three, four, five, six, seven, eight, or more of reported Raman shift peaks listed in the examples or in a figure can be used to characterize a particular chemical species.

Procedure for Powder X-Ray Diffraction (PXRD)

All powder x-ray diffraction patterns were obtained using the D/Max Rapid X-ray Diffractometer (D/Max Rapid, Contact Rigaku/MSC, 9009 New Trails Drive, The Woodlands, TX, USA 77381-5209) equipped with a copper source (Cu/K_{α}. 1.5406 angstroms), manual x-y stage, and 0.3 mm collimator. The sample was loaded into a 0.3 mm boron rich glass capillary tube (e.g., Charles Supper Company, 15 Tech Circle, Natick, MA 01760-1024) by sectioning off one end of the tube and tapping the open, sectioned end into a bed of the powdered sample or into the sediment of a slurried precipitate. Note, precipitate can be amorphous or crystalline. The loaded capillary was mounted in a holder that was secured into the x-y stage. A diffractogram was acquired (e.g., Control software: RINT Rapid Control Software, Rigaku Rapid/XRD, version 1.0.0, © 1999 Rigaku Co.) under ambient conditions at a power setting of 46 kV at 40 mA in reflection mode, while oscillating about the omega-axis from 0 - 5 degrees at 1 degree/s and spinning about the phi-axis at 2 degrees/s. The exposure time was 15 minutes unless otherwise specified. The diffractogram obtained was integrated over 2-theta from 2–60 degrees and chi (1 segment) from 0-360 degrees at a step size of 0.02 degrees using the *cyllnt* utility in the RINT Rapid display software (Analysis software: RINT Rapid display software, version 1.18, Rigaku/MSC.) provided by Rigaku with the instrument. The dark counts value was set to 8 as per the system calibration (System set-up and calibration by Rigaku); normalization was set to average; the omega offset was set to 180°; and no chi or phi offsets were used for the integration. The analysis software JADE XRD Pattern Processing, versions 5.0 and 6.0 (^{8}1995-2002, Materials Data, Inc.) was also used.

The relative intensity of peaks in a diffractogram is not necessarily a limitation of the PXRD pattern because peak intensity can vary from sample to sample, e.g., due to crystalline impurities. Further, the angles of each peak can vary by about +/- 0.1 degrees, preferably +/-0.05. The entire pattern or most of the pattern peaks may also shift by about

+/- 0.1 degree due to differences in calibration, settings, and other variations from instrument to instrument and from operator to operator. Any one or combination of two, three, four, five, six, seven, eight, or more of reported 2-theta angle peaks listed in the examples or in a figure can be used to characterize a particular chemical species.

Procedure for Differential Scanning Calorimetry (DSC)

An aliquot of the sample was weighed into an aluminum sample pan. (e.g., Pan part # 900786.091; lid part # 900779.901; TA Instruments, 109 Lukens Drive, New Castle, DE 19720) The sample pan was sealed either by crimping for dry samples or press fitting for wet samples (e.g., hydrated or solvated samples). The sample pan was loaded into the apparatus (DSC: Q1000 Differential Scanning Calorimeter, TA Instruments, 109 Lukens Drive, New Castle, DE 19720), which is equipped with an autosampler, and a thermogram was obtained by individually heating the sample (e.g., Control software: Advantage for QW- Series, version 1.0.0.78, Thermal Advantage Release 2.0, © 2001 TA instruments – Water LLC) at a rate of 10 degrees C /min from T_{min} (typically 20 degrees C) to T_{max} (typically 300 degrees C) (Heating rate and temperature range may vary, changes to these parameters will be indicated for each sample) using an empty aluminum pan as a reference. Dry nitrogen (e.g., Compressed nitrogen, grade 4.8, BOC Gases, 575 Mountain Avenue, Murray Hill, NJ 07974-2082) was used as a sample purge gas and was set at a flow rate of 50 mL/min. Thermal transitions were viewed and analyzed using the analysis software (Analysis Software: Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E; Build 3.1.0.40, © 1991 - 2001TA instruments – Water LLC) provided with the instrument.

Procedure for Thermogravimetric Analysis (TGA)

An aliquot of the sample was transferred into a platinum sample pan. (Pan part # 952019.906; TA Instruments, 109 Lukens Drive, New Castle, DE 19720) The pan was placed on the loading platform and was then automatically loaded into the apparatus (TGA: Q500 Thermogravimetric Analyzer, TA Instruments, 109 Lukens Drive, New

Castle, DE 19720) using the control software (Control software: Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0, © 2001 TA instruments – Water LLC). Thermograms were obtained by individually heating the sample at 10 degrees C /min from 25 degrees C to 300 degrees C (Heating rate and temperature range may vary, changes in parameters will be indicated for each sample) under flowing dry nitrogen (e.g., Compressed nitrogen, grade 4.8, BOC Gases, 575 Mountain Avenue, Murray Hill, NJ 07974-2082), with a sample purge flow rate of 60 mL/min and a balance purge flow rate of 40 mL/min. Thermal transitions (e.g. weight changes) were viewed and analyzed using the analysis software (Analysis Software: Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E; Build 3.1.0.40, © 1991 - 2001TA instruments – Water LLC) provided with the instrument.

Example 1

Celecoxib Sodium Salt from Aqueous Solution

To 1.787 g celecoxib was added 5.0 mL NaOH (1 M) and 5 mL of a solution of 1 M NaCl. The mixture was stirred and cooled to give slow crystallization of celecoxib Na salt. The solid was collected via filtration and washed with additional 1 M NaCl (10 mL). The solid was allowed to dry under flowing N_2.

TGA was performed on the sample by placing 7.149 mg of sample in the platinum pan. The starting temperature was 25 degrees C with aheating rate of 10 degrees C/minute, and the ending temperature was 300 degrees C. The resulting thermogram is shown in Fig. 1. The thermogram shows a mass loss of about 9.0 % between about 25 and about 140 degrees C, attributed to the loss of about 2.1 equivalents of water. The hydration state of the salt can vary depending on the humidity, temperature, and other conditions.

The PXRD diffractogram for the compound prepared above is shown in Fig. 2. The diffractogram has characteristic peaks that can be used to characterize the salt comprising any one, or any combination of any two, any three, any four, any five, any six, or any other combination of peaks at 2-theta angles in Fig. 2 including, for example, the peaks at 3.65, 8.95, 10.77, 11.43, 14.01, 17.19, 18.33, 19.47, 19.99, 20.61, 21.71, 22.57, and 25.81 degrees.

Example 2

Celecoxib Sodium Salt from Isopropanol Solution

To 126.3 mg of celecoxib was added a 1.0 mL aliquot of isopropanol, and the mixture was heated to dissolve the celecoxib. Sodium ethoxide was added as a solution (21%) in ethanol (0.124 mL solution, 3.31×10^{-4} mol sodium ethoxide). An additional 1.0 mL of isopropanol was added. The mixture was stirred to obtain a slurry of white crystalline solids that appeared as fine birefringent needles by polarized light microscopy.

The slurry was filtered by suction filtration and rinsed with 2 mL of isopropanol. The solid was allowed to air dry before being gently ground to a powder. The product was analyzed by PXRD, DSC, and TGA as in Example 1, but a 0.5 mm capillary was used to hold the sample in the PXRD experiment. The compound lost 17.35 % weight between room temperature and 120 degrees C. The DSC thermogram shows a broad endothermic region, which is consistent with a loss of volatile components with increasing temperature. The endotherm peaks at 66 degrees C. The PXRD pattern peaks that can be used to characterize the salt include any one or combination comprising any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, any eleven, any twelve, or all thirteen 2-theta angles of 4.09, 4.99, 6.51, 7.07, 9.99, 11.59, 16.53 , 17.69 , 18.47 , 19.13 , 20.11 , 20.95 , 22.67 degrees, or any one or combination of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13 peaks of Fig. 62.

Example 3

Celecoxib Sodium Salt from Aqueous Solution

Synthesis 1: To a vial was added 29.64 mg celecoxib and 3.00 mL of 1 M sodium hydroxide. The celecoxib dissolved. After a time, the celecoxib precipitated from solution.

Synthesis 2: To a vial was added 7.10 mg celecoxib and 3.00 mL of 1 M sodium hydroxide. The celecoxib dissolved. Overnight, the celecoxib precipitated and formed white, needle-like crystals.

Synthesis 3: To a vial was added 17.6 mg celecoxib and 10 mL of 1 M sodium hydroxide. The celecoxib dissolved. The vial was placed in a beaker wrapped in aluminum foil and filled with a large tissue for insulation. The beaker was left and crystals formed within about 12-36 hours.

Analysis: The product solids from syntheses 1 and 2 were combined and analyzed by PXRD, DSC, and TGA as in example 1, but a 0.5 mm capillary was used to hold the sample in the PXRD experiment. The product salt was found to contain about 4 equivalents of water per equivalent of salt, although as stated herein the hydration state of the salt can vary depending on humidity, temperature, and other conditions. TGA showed a weight loss of 14.9% as the temperature was increased from room temperature to 100 degrees C at 10 degrees C/min. DSC analysis showed a large endothermic transition at 74 +/- 1.0 degrees C and a second broad and noisy endothermic transition at about 130 +/- 5.0 degrees C. The PXRD pattern has peaks that can be used to characterize the salt by including any one or a combination comprising any two, any three, any four, any five, or all six 2-theta angle peaks of 3.6, 8.9, 9.6, 10.8, 11.4, and 20.0 degrees.

Example 4

Pharmacokinetic Studies in Rats

The sodium salt form (from Example 6) was compared with CELEBREX powder in terms of absorption in rats (Figs. 4A and 4B).

Pharmacokinetics in male Sprague-Dawley rats after 5 mg/kg oral doses of the celecoxib crystal form used in the marketed formulations and the sodium salt form are shown in Fig. 4A and 4B. Solids were placed in size 9 gelatin capsules (Torpac) and dosed via gavage needle, followed by oral gavage of 1 mL water. CELEBREX granulation was transferred from commercial 200 mg capsules. The sodium salt was blended with polyvinylpyrrolidone (e.g. PovidoneK30) in a 1:4 mixture. The plots are averages of plasma levels at each of the time points from plasma of 5 rats.

The pharmacokinetics at 5 mg/kg doses of the celecoxib sodium salt demonstrate a faster peak level of the drug in plasma. Early timepoints show higher levels of celecoxib in plasma from the sodium salt relative to CELEBREX (in particular, see Fig. 4A).

Example 5

Solubility of Celecoxib Sodium Salt in the Presence of Polyvinylpyrrolidone

Water was added to a 1:4 mixture of celecoxib sodium salt and polyvinylpyrrolidone (PVP) to obtain a clear solution. The solution was stable for at least 15 minutes, after which time, crystals of neutral celecoxib began to form.

Crystalline neutral celecoxib did not dissolve when added to aqueous polyvinylpyrrolidone or when water was added to a dry blend of neutral crystalline celecoxib and polyvinylpyrrolidone.

Example 6

Preparation of Celecoxib Sodium Salt

The free acid of celecoxib (5.027 g) was suspended in an aqueous solution of NaOH (13.181 mL, 1 M). The suspension was gently heated at 60 degrees C for 1 minute to dissolve the remaining solid. The mixture was allowed to cool to room temperature, which yielded no precipitation. Further cooling in an ice bath for 1 hour gives precipitation of the product. The resulting solution was filtered and allowed to air dry.

Characterization of the product has been achieved via TGA, DSC, PXRD, Raman spectroscopy, microscopy, and ^{1}H NMR spectroscopy. NMR acquisitions were performed on a Varian 300 MHz Spectrometer in dimethyl sulfoxide-d^{6}.

The PXRD pattern has characteristic peaks as shown in Fig. 13A. An intense peak can be seen at 19.85 with other peaks at 2-theta angles including but not limited to, 3.57, 10.69, 13.69, 20.43, 21.53 and 22.39. The crystal can be characterized by any one, any two, any three, any four, any five, or all six of the peaks above, or any one or combination of any number 2-theta angles of Fig. 13A.

Results of Raman spectroscopy can be seen in Fig. 13B. Raman shift (cm^{-1}) peaks occur at positions including, but not limited to, any one, any two, any three, any four, all five of 1617.11, 1446.20, 1373.73, 975.02 and 800.15 cm^{-1}, or any combinations of 2, 3, 4, 5 or more peaks of Fig. 13B.

Example 7

Administration of Celecoxib Compositions to Dogs

The celecoxib salt of Example 6 was administered to dogs and compared to administration of commercially available celecoxib. Six male beagle dogs aged 2-4 years old and weighing 8-12 kg were food-deprived but were given water. Each of the dogs was administered 3 test doses as described below and allowed a one week washout period between doses. The test doses were: (1) commercially available celecoxib in the form of CELEBREX at 1 milligrams per kilogram (mpk) combined with 70/30 PEG400/water which was administered intravenously, (2) oral dose of commercially available celecoxib in the form of CELEBREX at 5 mpk adjusted for each dog's weight in size 4 gelatin capsules, and (3) oral dose of the sodium salt of the present invention as prepared according to Example 6 at 5 mpk adjusted for each dog's weight in size 4 gelatin capsules. Blood samples of approximately 2 mL in sodium heparin were obtained by jugular venipuncture at 0.25, 0.5, 1, 3, 4, 6, 8, 12, and 24 hours post-dose. Additional samples were obtained predose and at 0.08 hr for the IV study. Blood samples were immediately placed on ice and centrifuged within 30 minutes of collection. Plasma samples (~1.0 mL) were harvested and stored in 4 aliquots of 0.25 mL at -20 degrees C. Plasma samples were analyzed for celecoxib using an LC-MS/MS assay with a lower limit of quantitation of 5 ng/mL. Pharmacokinetic profiles of celecoxib in plasma were analyzed using the PhAST software Program (Version 2.3, Pheonix Life Sciences, Inc.). The absolute bioavailability (F) is reported for oral doses relative to the IV dose.

Fig. 5 shows the mean pharmacokinetic parameters (and standard deviations therefore) of celecoxib in the plasma of male dogs following a single oral or single intravenous dose of celecoxib or celecoxib sodium salt. The maximum blood serum concentration and bioavailability of orally-administered celecoxib sodium salt was about three- and two-fold greater, respectively, than a roughly equal dose of orally-administered celecoxib, and the maximum blood serum concentration of celecoxib sodium was reached 40% faster than for celecoxib.

Example 8

Celecoxib Lithium Salt Preparation Method: MO-116-49B

To 100 mg of commercially available celecoxib was added 0.35 M LiOH (aq) (Lithium Hydroxide Monohydrate – Aldrich Cat# 25,427-4, Lot 00331K1) solution with a lithium:celecoxib ratio of 1.53:1 in a vial with a Teflon coated silicon rubber septum cap. The mixture was gently heated during dissolution with occasional swirling until all solids dissolved. Dry nitrogen was blown over the solution for 2 days through stainless steel needles inserted into the septum cap until the solution was dry. Characterization of the product was achieved via DSC (Fig. 14), TGA (Fig. 15), Raman spectroscopy (Fig. 16) and PXRD (Fig. 17).

Celecoxib Lithium Salt Data (DSC)

1.56 mg of collected sample was placed into an aluminum DSC pan with cover. During heating, 50 mL/min nitrogen purge gas was used. Results of the DSC thermogram (Fig. 14) show a melting point at 111.84 degrees C and a second endotherm, less sharp at 237.11 degrees C.

Celecoxib Lithium Salt Data (TGA)

8.229 mg of collected sample was placed into a platinum TGA pan. Results of the TGA (Fig. 15) demonstrated about a 14% weight loss between about 25 degrees C and 190 degrees C.

Celecoxib Lithium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman spectrometer. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 micrometer slit
	Sample position: Microscope
	Camera temperature: -50 degrees C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

Results of Raman spectroscopy show multiple spectral peaks that can be used to characterize the salt. These include any one, any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, or any other combination of peaks of Figure 16, e.g., 1617.10, 1596.95, 1449.56, 1374.03, 1115.24, 1062.85, 976.50, 800.67, 740.91 and 633.94 cm^{-1}.

Celecoxib Lithium Salt Data (PXRD)

A small amount of collected sample was placed in a 0.3 mm glass PXRD tube. The tube was placed into a Rigaku D/Max Rapid PXRD and set to: Cu; 46 kV/40 mA; Collimator: 0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was 15 minutes. The PXRD pattern has characteristic peaks as shown in Fig. 17. PXRD peaks that can be used to characterize the salt include any one, or combination of any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, any eleven, or any other combination of peaks from Fig. 17, e.g., 4.14, 9.04, 10.705, 12.47, 15.08, 15.75, 18.71, 19.64, 20.52, 21.55 and 23.00 degrees.

Example 9

Celecoxib Potassium Salt: Preparation Method MO-116-49A

100 mg of celecoxib was dissolved in a 0.35 M KOH (aq) solution (Potassium Hydroxide – Spectrum, Cat# P0180, Lot# PN0690) with a potassium:celecoxib ratio of 1.40:1 in a vial with a Teflon coated silicon rubber septum cap. The resulting solution was gently warmed during dissolution with occasional swirling until all solids dissolved. After all solids were dissolved, the solution was dried by flowing dry nitrogen over the solution for 2 days through stainless steel needles inserted into the septum cap. Analysis of the resulting product was performed. Characterization of the product was achieved via DSC (Fig. 18,) TGA (Fig. 19), Raman spectroscopy (Fig. 20) and PXRD (Fig. 21).

Celecoxib Potassium Salt (MO-116-49A) Data (DSC)

1.119 mg of collected sample was placed into an aluminum DSC pan with cover. The results are depicted in the graph of Fig. 18 and show a melting point endotherm at 87.39 degrees C.

Celecoxib Potassium Salt (MO-116-49A) Data (TGA)

5.989 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated 10 degree C/min to 90 degree C, held for 10 minutes, ramped 10 degree C/min to 300 degree C, and held for 10 minutes with 40mL/min nitrogen purge gas. The results are depicted in Fig. 19 and show a 5.778% weight loss between 25 and 200 degrees C. A shoulder in the data is seen at 80 degrees C. Weight loss before this point is due to unbound water. The weight loss between 80 and 200 degrees C is due to more closely bound water, and represents 0.64 equivalents of water.

Celecoxib Potassium Salt (MO-116-49A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman spectrometer. The sample capture was set to 6 background scans and 12 sample collections. The parameters used for this analysis were:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 micrometer slit
	Sample position: Microscope
	Camera temperature: -50 degrees C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

The results are depicted in Fig. 20 and show characteristic Raman shift (cm^{-1}) peaks at positions including, but not limited to any one or combination of any two, any three, any four, or all five of the peaks: 1617.66, 1448.22, 1374.09, 976.28, and 801.60 cm^{-1}, or any combinations of 1, 2, 3, 4, 5, or more peaks of Fig. 20.

Celecoxib Potassium Salt (MO-116-49A) Data (PXRD)

A small amount of collected sample was placed in a 0.3 mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46 kV/40 mA; Collimator: 0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was 15 minutes. The PXRD pattern has characteristic peaks as shown in Fig. 21. Peaks can be seen at 2-theta angles including, but not limited to, 4.03, 12.23, 15.35, and 19.79 degrees. The crystal can be characterized by any one or combination of any two, any three, or all four of the above angles or any one or any number combination of 2-theta angles of Fig. 21.

Example 10

Celecoxib Potassium Salt: Preparation Method MO-116-55D

An alternative method of preparing a celecoxib potassium salt of the instant invention was performed. 100 mg of celecoxib (commercially available) was dissolved in 2.2 mL toluene and 0.1 mL methanol in a vial with a TEFLON® coated silicon rubber septum cap. The solution was warmed gently during dissolution with occasional swirling until all solids were dissolved. 1.03 equivalents of KOH (Potassium Hydroxide – Spectrum, Cat# P0180, Lot# PN0690) was added to the solution using a 3 M KOH (aq) solution. After the resulting phase separation, the bottom phase was removed and was dried by flowing dry nitrogen over the solution for 1 day through stainless steel needles inserted into the septum cap.

Analysis was performed. Characterization of the product was achieved via TGA (Fig. 22), Raman spectroscopy (Fig. 23), and PXRD (Fig. 24).

Celecoxib Potassium Salt (MO-116-55D) Data (TGA)

5.447 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated 10 degree C/min to 90 degree C, held for 10 minutes, ramped 10 degree C/min to 300 degree C, and held for 10 minutes with 40 mL/min nitrogen purge gas. The results are depicted in Fig. 22 and show a weight loss of about 4.9 wt % from 25 degrees C to 200 degrees C and a weight loss of about 2.9 wt % at a shoulder from about 70 degrees C to 200 degrees C. Initial weight loss before the shoulder is most likely due to the evaporation of methanol. The weight loss after the shoulder is most likely due to excess water.

Celecoxib Potassium Salt (MO-116-55D) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman spectrometer. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters of the spectrometer were as follows:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 micrometer slit
	Sample position: Microscope
	Camera temperature: -50 degrees C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

The results are depicted in Fig. 23 and show characteristic Raman shift (cm^{-1}) peaks at positions including, but not limited to any one or a combination of any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, or all eleven of the peaks 1615.51, 1446.09, 1374.28, 1232.91, 1197.04, 1108.99, 1060.94, 973.01, 798.86, 739.82, or 633.37 cm^{-1}, or any one or combinations of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more peaks of Fig. 23.

Celecoxib Potassium Salt (MO-116-55D) Data (PXRD)

A small amount of collected sample was placed in a 0.3 mm glass PXRD tube. The tube was placed into a Rigaku D/Max Rapid PXRD set to Cu; 46 kV/40 mA; Collimator: 0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was 15 minutes. The results are depicted in Fig. 24.

Example 11

Celecoxib Calcium Salt: Preparation Method MO-116-62A

100 mg of celecoxib (commercially available) was dissolved in a 1 M NaOH methanol solution at a 1:1 ratio of NaOH:celecoxib in a vial and heated gently with occasional swirling until all solids were dissolved. 3 M $CaCl_2$ in methanol was added to achieve a ratio of 1.5:1 Ca^{2+} ions to celecoxib. The precipitate was filtered with a centrifuge tube filter (Corning Inc. Costar (0.22 micron) #8169) in an eppendorf centrifuge (5415D) set at 12,000 rpm for 5 minutes. The upper section of the eppendorf tube containing the solids was placed into a vial with a rubber septum cap. The powder was dried overnight by flowing dry nitrogen into the vial through stainless steel needles inserted into the septum cap.

Analysis was performed. Characterization of the product was achieved via TGA (Fig. 25), Raman spectroscopy (Fig. 26), and PXRD (Fig. 27).

Celecoxib Calcium Salt (MO-116-62A) Data (TGA)

3.414 mg of collected sample was placed into a platinum TGA pan. The pan was placed in TA Instruments Q500 TGA and heated 10 degrees C/min to 90 degrees C, held for 10 minutes, ramped 10 degree C/min to 300 degree C, and held for 10 minutes with 40 mL/min nitrogen purge gas. Results (Fig. 25) show a weight loss of about 4.2 % between 25 and 200 degrees C and about 3.2 % between 70 and 200 degrees C. Initial weight loss below 70 degrees C is due to unbound solvent. The shoulder seen after 70 degrees C is due to the loss of more closely bound methanol and represents 0.45 equivalents of methanol.

Celecoxib Calcium Salt (MO-116-62A) Data (Raman)

A small quantity of collected sample was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman spectrometer. The sample capture was set to 6 background scans and 12 sample collection scans.

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 micrometer slit
	Sample position: Microscope
	Camera temperature: -50 degrees C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

Characteristic Raman shift (cm^{-1}) peaks were observed at positions including, but not limited to, any one, any two, any three, any four, any five, any six, or all seven of the peaks 1616.99, 1598.42, 1450.05, 1376.57, 973.10, 800.62, 642.20, or any combinations of 2, 3, 4, 5, 6, 7 or more peaks of Fig. 26.

Celecoxib Calcium Salt (MO-116-62A) Data (PXRD)

A small amount of collected sample was placed into a 0.3 mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46 kV/40 mA; Collimator: 0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was 15 minutes. An intense peak was observed at 2-theta angle of 31.67 and lesser peaks at 7.82, 9.27, 20.56, and 27.35. Any one or a combination of 2, 3, 4, or 5 of the preceding peaks can be used to characterize the salt, as well as, any 1, 2, 3, 4, 5, 6, or more peaks of Fig. 27.

Example 12

Comparative Analysis of Neutral Celecoxib

To aid in the analysis of some of the data retrieved, commercially available celecoxib was subjected to the same analytical techniques of powder X-ray diffraction (PXRD) and Raman spectroscopy. The results were used as a comparison for the salts of the present invention.

Comparison Data: Celecoxib (PXRD)

A small amount of commercially available celecoxib was placed in a 0.3 mm glass PXRD tube. The tube was placed in Rigaku D/Max Rapid PXRD set to Cu; 46 kV/40 mA; Collimator: 0.3; Omega-axis oscillation, Pos(deg) 0-5, speed 1; Phi-axis spin, Pos 360, Speed 2; Collection time was 15 minutes. The results are depicted in Fig. 28.

Some of the peaks of the free acid may also be found in the compositions of the present invention. As a further means of characterizing the compositions of the present invention, the peaks characteristic of the free acid, as shown in Fig. 28, may also be specifically excluded from compositions of the present invention.

Comparison Data: Celecoxib (Raman)

A small quantity of commercially available celecoxib was placed on a glass slide and mounted in the Thermo Nicolet Almega Dispersive Raman spectrometer. The sample capture was set to 6 background scans and 12 sample collection scans. The parameters were as follows:

DATA COLLECTION INFORMATION	SPECTROMETER DESCRIPTION
Exposure time: 2.00 sec	Spectrometer: Visible Raman Microscope
Number of exposures: 12	Laser: 785 nm
Number of background exposures: 6	Laser power level: 100%
	Laser polarization: Parallel
	Grating: 360 lines/mm
	Spectrograph aperture: 100 micrometer slit
	Sample position: Microscope
	Camera temperature: -50 degrees C
	CCD rows binned: 89-150
	CCD binning: On chip
	RIM position: Mirror
	Polarization analyzer: Out
	Illuminators: Of

The results are depicted in Fig. 29.

Example 13

Solid-state Formulations of Celecoxib Sodium Salt Hydrate

Solid-state formulations based on selected PLURONIC excipients in combination with hydroxypropylcellulose (HPC) and the crystalline celecoxib sodium hydrate salt, prepared using traditional mortar and pestle technique, showed enhanced dissolution of the celecoxib salt in simulated gastric fluid.

This example demonstrates that related solid-state formulations enhance the dissolution and retard the precipitation of celecoxib salts as compared to the celecoxib neutral free acid compound. The processes used to identify and test the preferred excipients in these examples are two-fold: (1) A "crystal retardation assay" was used to identify excipients that supersaturate celecoxib in solution; and (2) In-vitro dissolution studies were performed on selected excipients to verify the "crystal retardation assay" results.

Example 14

Crystal Retardation Assay

Crystal Retardation Assay - Method

1. 57 excipients according to Table 3 were prepared at a concentration of 2 mg/mL (0.2 % by weight) in simulated gastric fluid having 200 mM hydrochloric acid and dispensed in quadruplicate in 96-well plates at a volume of 150 microliters. Two controls were used: (a) Simulated gastric fluid lacking excipients; and (b) Simulated gastric fluid containing 2 mg/mL Vitamin E TPGS and 2 mg/mL HPC. The latter control was chosen because of prior indication that this excipient combination provides enhanced dissolution of celecoxib sodium hydrate. Simulated gastric fluid was prepared by adding 2 g/L sodium chloride and 1 g/L Triton X-100 to DI H_20. 200 mM hydrochloric acid was added to adjust and buffer the pH.

Table 3.

Excipients used in Recrystallization/precipitation Retardation Assay		
2 Ethoxyethanol	Polyethyleneglycol Monooleate (Mapeg 400-MO)	PLURONIC P123
Alkamus 719		
Alkamus EL 620	Polyethyleneglycol 300	PLURONIC P85
Alkamus EL 719	PLURONIC 17R2	Poloxamer 188
Benzyl Alcohol	PLURONIC F108	Poloxamer 338
Cremophor EL	PLURONIC F127	Polypropyl 52
Cremophor RH40	PLURONIC F38	Polysorbate 40
Crillet 1 HP	PLURONIC F68	Polysorbate 80
Crovol A-70	PLURONIC F77	Propylene Glycol
Ethosperse G-26	PLURONIC F87	Polyvinylpyrrolidone 10K
Ethylene Glycol	PLURONIC F88	Polyvinylpyrrolidone 360K

Glycerin	PLURONIC F98	Polyvinylpyrrolidone 55K
HEC 250K		Saccharin
Hydroxypropylcellulose (HPC)	PLURONIC L31	Sodium lauryl sulphate
Isopropanolamine	PLURONIC L43	Tagat 02
Myrj 52	PLURONIC L44	Transcutol P
Polyethyleneglycol 1000	PLURONIC L92	Triacetin
Polyethyleneglycol 200	PLURONIC P103	Triethanol amine
Polyethyleneglycol 400	PLURONIC P104	Vitamin E TPGS
Polyethyleneglycol 600	PLURONIC P105	Vitamin E TPGS & HPC

2. The 96-well plates were sealed, and incubated to a temperature of 40 degrees C for 20 minutes. After incubation, the plate seals were removed.

3. Celecoxib, pre-dissolved in potassium hydroxide to a concentration of 5.5 mg/mL, was dispensed in 15 microliter aliquots to each well and immediately mixed. This gave a final celecoxib concentration of 0.5 mg/mL in each well. The final excipient concentration was 1.8 mg/mL.

4. A nephelometer (Nephelostar Galaxy, BMG Technologies, Durham, NC), with a chamber preheated to 37 degrees C, was used to analyze the ability of the excipients to retard the crystallization/precipitation of supersaturated celecoxib. The assay plate containing celecoxib and excipients was sealed using an optically clear seal and placed into the nephelometer instrument. The nephelometer recorded changes in solution turbidity over a 1 hour time period. Solutions that displayed an increased turbidity over a baseline indicated that celecoxib had precipitated out solution.

Crystal Retardation Assay - Results:

Fig. 30 shows crystal retardation time for celecoxib as a function of excipient in simulated gastric fluid (SGF). Final concentration of celecoxib was 0.5 mg/mL. Black

bars indicate crystal retardation time that may be greater than 60 min. Excipients listed in Table 3, but excluded from Fig. 30 did not show any appreciable crystal retardation time (i.e., greater than 1.5 minutes). Nineteen of 58 excipients were found to retard recrystallization/precipitation of celecoxib. Interestingly, in contrast to the dissolution assay, Vitamin E TPGS alone had a longer retardation time than in combination with HPC, which alone did not show any retardation time.

Importantly, formulations that increase the solubility of a drug will not necessarily increase its dissolution. For example, according to PCT application WO 01/78724, the solubility of celecoxib free acid in Transcutol P is 350 mg/g. It was found that in contrast to enhancing solubility, Transcutol P does not enhance dissolution of the free acid. Transcutol P does extend the time to T_{max} and increases the time the concentration of celecoxib is above ½ T_{max} when used in combination with a precipitation retardant and enhancer. It was further found that dissolution of a salt form is far superior to the dissolution of compositions comprising the free acid.

The presence of six PLURONIC (poloxamer) excipients among successful precipitation retardants prompted further study of these compounds. PLURONICs are ethylene oxide - propylene oxide block copolymers, whose properties can be significantly altered (i.e., melting point, cloud point, molecular weight, HLB number, surface tension, interfacial tension, etc.) by adjusting the ratio of copolymer blocks. Further examination of these properties showed that the surface tension of these copolymers at a 0.1 % concentration in water correlates with the ability to retard the crystallization/precipitation of celecoxib. PLURONIC excipients having low interfacial tension (i.e., less than about 10 dyne/cm) or having a surface tension less then about 42 dyne/cm were more effective at keeping celecoxib in solution than PLURONIC excipients having high interfacial tension or surface tension. This observation is illustrated in Fig. 31, along with interfacial data for PLURONICs that were not tested. Based on this correlation, the supersaturation properties of these additional PLURONICs also correlate with interfacial tension.

Fig. 31 shows interfacial tension of selected PLURONIC excipients in water. PLURONIC excipients having low interfacial tension correlate with excipients that retard crystallization/precipitation of celecoxib in simulated gastric fluid. An interfacial tension threshold for crystal retardation was loosely defined as less than about 9 or 10 dyne/cm.

Excipient concentration in the assay was 0.18 %; celecoxib concentration was 0.5 mg/mL. Interfacial data obtained from BASF at 0.1 % concentration in water versus mineral oil at 25 degrees C. (PLURONIC is a trademark of BASF).

Example 15

In Vitro Dissolution Studies of PLURONIC Excipients

In Vitro Dissolution Studies of PLURONIC Excipients - Method

1. Celecoxib Preparation
    a. Fresh celecoxib sodium salt hydrate was prepared and analyzed to be approximately 90% free acid vs. sodium content.
    b. The celecoxib salt was ground using mortar and pestle until fine powder was formed. The fine powder was sieved using a 105 micrometer pore size mesh and stored in a 20 mL scintillation vial at room temperature.
2. Formulation Preparation
    a. Fresh PLURONIC excipient was dispensed into a mortar. If initially a solid at room temperature, the PLURONIC was ground until a smooth powder was formed.
    b. If HPC was to be added, it was dispensed after the PLURONIC excipient. The HPC was combined with the PLURONIC and the two were ground together using a pestle and mixed with a spatula for 1 minute.
    c. 105 micrometer sieved celecoxib salt was added to mortar and the mixture was ground and mixed for several minutes.
    d. If needed, a liquid excipient such as Poloxamer 124, Peg 200, or Peg 400 was added to the mortar as a granulating fluid-like liquid to form an intimate contact between drug and excipient. The mixture was ground and mixed until a uniform consistency was observed in the solid-state mixture.
3. Dissolution Assay
    a. A water bath was set up at 37 degrees C.

b. Simulated gastric fluid in the fasted state (SGF) was prepared at pH 1.7 and diluted five times with deionized water. The final pH was approximately 2.4. The simulated gastric fluid was diluted five times to simulate the effect of drinking a glass of water with the medication. The SGF was pre-heated to 37 degrees C.

c. The formulation was placed in a 20 mL scintillation vial.

d. A 10 mm x 3 mm stir bar was added.

e. Diluted SGF was added to the formulation. The volume added was set to satisfy a 2 mg/mL dose of celecoxib free acid.

f. The vial was placed in the water bath and allowed to stir.

g. At each time point, 0.9 mL of solution was extracted and filtered through a 0.2 micrometer polyvinylflouridine filter. The first 2/3 of filtrate was discarded as waste and the last 1/3 was collected into an eppendorf tube. 0.1 mL of the collected filtrate was immediately transferred to an autosampler vial and diluted ten times with 0.9 mL of methanol. The autosampler vials were crimp sealed and submitted for content analysis using high performance liquid chromatography with ultraviolet detection.

In Vitro Dissolution Studies of PLURONIC Excipients - Results:

1. Dissolution of two PLURONIC excipients that had low interfacial tension: PLURONIC P123 and F127. PLURONIC P123 was a paste at room temperature, and resulted in sticky formulation of celecoxib salt. PLURONIC F127 was a solid at room temperature and formed a flowable powder solid-state mixture with the celecoxib salt. The dissolution result for these mixtures at equal weight concentrations of excipient to celecoxib free acid content are shown in Figure 32. PLURONIC P123 gave enhanced dissolution of celecoxib salt, while PLURONIC F127 did not. The poor performance of PLURONIC F127 in enhancing celecoxib dissolution was due to the slow dissolution of the excipient. In contrast, PLURONIC P123 was intimately bound with the celecoxib salt in a "sticky" waxy mass, which delayed the dissolution of celecoxib. This allowed the excipient to dissolve to a greater extent prior to the full dissolution of the celecoxib salt form.

2. Dissolution of celecoxib sodium hydrate was performed in the presence of HPC using PLURONIC P123, PLURONIC F127, and PLURONIC F87; PLURONIC F87 has a high interfacial tension value. Equal weight concentrations of PLURONIC and HPC to celecoxib free acid content were used in the formulations. The PLURONIC P123 formulation was sticky due to the pasty nature of the excipient. The PLURONIC F127 and F87 formulation were flowable since these excipients are solids at room temperature. Dissolution data for these formulations are shown in Fig. 33. The data showed that addition of HPC in the PLURONIC P123 formulation produced a widening of the dissolution profile. In the PLURONIC F127 formulation, HPC enhanced the initial dissolution component of the profile (i.e. < 10 minutes). In contrast, no dissolution profile was observed in the PLURONIC F87 formulation. Since PLURONIC F87 has a high interfacial tension (17.4 dyne/cm), the resulting data supports the correlation of precipitation retardants with interfacial tension. Since the PLURONIC P123 formulation (i.e., sticky) showed a dissolution profile that was enhanced to a greater extent than the PLURONIC F127 formulation (i.e., loose powder) in terms of time to recrystallization/precipitation, it was hypothesized that the addition of an excipient that physically binds the components of the PLURONIC F127 formulation will result in further dissolution enhancement.

3. Dissolution of celecoxib sodium hydrate using PLURONIC F127 and HPC was performed using a granulated fluid-like liquid to bind the solid-state mixture. Three granulating fluid-like liquids were chosen: Peg 200, Peg 400, and Poloxamer 124. Equal weight ratios of celecoxib free acid content, PLURONIC F127, and HPC were formulated with 40-45% celecoxib free acid weight of granulating fluid. The effect of these formulations on dissolution is shown in Fig. 34. The granulating fluid-like liquids increased the dissolution of celecoxib, possibly by delaying the contact between the celecoxib salt and the dissolution media until PLURONIC F127 had been dissolved to a significant extent.

Dissolution of celecoxib sodium hydrate was then measured from a compacted formulation containing PLURONIC F127 and HPC excipients. Formulations containing equal weight ratios of celecoxib free acid content, PLURONIC F127, and HPC were mixed and compacted into 6 mm discs at 4900 psi. Dissolution results, shown in Fig. 35, indicated enhanced dissolution with onset retarded by approximately 15-20 minutes. The compaction process produced a similar effect on dissolution to that observed by the addition of a granulating fluid (see Fig. 34) with the addition of a controlled release mechanism. The controlled release characteristic of the profile can be modulated by selecting HPC or HPMC with varying grades of viscosity and the addition of disintegrants into the compact. Compacts are attractive formulations due to their lower production cost and fewer processing steps.

Example 16

General Method of Crystal Retardation Assay

The methods described above are specific examples of general methods of the present invention aimed at identifying excipients that retard the nucleation of solid-state API, their derivatives, and other non-pharmaceutical compounds of marketable interest from a solution supersaturated with API. The method is outlined in Fig. 36 and is described as follows:

1. Excipients are dissolved to a desired concentration in de-ionized (DI) water or other media (i.e., simulated gastric or intestinal fluids).
2. API is dissolved in a suitable solvent in which it has high solubility (i.e., acidic pH environment for free base type API; and basic pH environment for free acid type API).
3. The excipient solutions are dispensed into an assay plate (i.e., 96-well or 384-well optically clear plate) either manually or using automated liquid handling equipment. The excipients can be added as single, binary, ternary, or higher order excipient combinations into each well. An example of a liquid handling instrument is the Tecan Genesis (Tecan U.S. Inc, Research Triangle Park, NC).

4. The API solution is dispensed into the assay plate. The API solution can be dispensed one well at a time, by rows, or columns using the Tecan Genesis instrument or simultaneously into all wells using the Tecan Genmate instrument. The volume of API solution added is restricted to a small size to avoid causing any shifts in the properties of the excipient solution.
5. The solutions are mixed to uniformly distribute the API throughout the excipient solution. The plate is sealed and incubated at a desired temperature.
6. Onset of solid-state nucleation is determined using an instrument capable of measuring scattered light. Examples of scattered light measurement capable instruments are the NepheloStar nephelometer (BMG Technologies, Durham, NC) and the SPECTRAmax PLUS plate reader (Molecular Devices Corp, Sunnyvale, CA). Temperature is maintained at a constant pre-defined set point by the incubation features of the instruments.
7. Birefringence screening, PXRD, etc. may be performed to determine if precipitated API is amorphous or crystalline. If the API is crystalline, crystal habit and particle size can be recorded.
8. The data are analyzed and the excipients are ranked according to their respective retardation times.
9. Informatics may be used to correlate successful excipients that retard nucleation with physical property information.

Typical information obtained from the methods:

1. Solid-state retardation time as a function of excipient
2. Qualitative measure of crystallization/precipitation kinetics as a function of excipient
3. API final solid-state form analysis (i.e., amorphous, crystalline, habit) in excipient solutions

Example 17

Illustration of Resulting Crystal Retardation Data

Goal: Identify excipients that retard the solid-state nucleation of *Compound A* in *Fluid F* at a temperature of 37 degrees C.

Method:

1. 24 excipient solutions were prepared at a concentration of 16 mg/mL in DI water.
2. *Fluid F* was prepared in DI H_20 by mixing ingredients at twice the desired final concentration.
3. API solution was prepared at a concentration of 5.5 mg/mL in *Fluid C*.
4. The Tecan Genesis instrument was used to dispense a combination of 75 microliters *Fluid F*, 18.75 microliters excipient solution, and 56.25 microliters DI H_20 into each well of a 96-well plate. The final concentration of excipient in each well was 2 mg/mL in *Fluid F*. The total fluid volume per well was 150 microliters. Four replicate wells were used for each single excipient solution. An example of the layout is shown in Fig. 37.
5. The plate was sealed using a transparent seal (Part No. 6575; Corning Incorporated, Corning, NY) and incubated at 40 degrees C for 20 minutes.
6. The seal was removed and 15 microliters of API solution was dispensed simultaneously into all 96-wells. The final concentration of API in each well was 0.5mg/mL. (Note: The time dependence for solid-state nucleation began as soon as the API solution was added.)
7. The well contents were mixed and sealed using the transparent seal (Part No. 6575; Corning Incorporated, Corning, NY).
8. The plate was placed on the Nephelostar instrument to collect light scatter data over a 1 hour time period. The Nephelostar incubated the plate at 37 degrees C as specified in the goal of the assay.
9. At the end of the assay, the data were analyzed using Microsoft Excel and retardation times were calculated. An example of collected light scatter data is shown in Figure 38. Onset of solid-state nucleation is defined as the time when the

light scatter signal increases above the baseline signal. The threshold limit for the increase of the light scatter signal used to define a precipitation/crystallization event is usually set at three times the standard deviation of the baseline signal to take into account background noise. The threshold can be set however, to a different value depending on the sensitivity of the assay and the desired limit of precipitation/crystallization.

10. The retardation times (if any) for the excipient solutions were ranked. Figure 30 shows a graphical representation of the ranking.

Non-limiting examples of alternatives to this general method include:

1. Retardation time can be measured as a function of excipient concentration.
2. Retardation time can be measured as a function of API salt or co-crystal concentration.
3. API can be concentrated in a non-aqueous medium prior to assay.
4. Temperature can be varied and controlled according to a desired specification.

Instead of mixing the compound solution with the excipient solution, the test excipient can be mixed with the API in the compound solution prior to combining with the aqueous/SGF/SIF or other test solution (which is the excipient solution minus the excipient).

Example 18

Propylene Glycol Solvate of Celecoxib Sodium Salt

A propylene glycol solvate of the sodium salt of celecoxib was prepared. To a solution of celecoxib (312 mg; 0.818 mmol) in Et_2O (6 mL) was added propylene glycol (0.127 mL, 1.73 mmol). To the clear solution was added NaOEt in EtOH (21%, 0.275 microliter, 0.817 mmol). After 1 minute, crystals began to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The off-white solid was then air-dried and collected. The crystal formed was a 1:1 solvate. The solid was characterized by TGA and PXRD. The results are depicted in Fig. 39 and 40.

Fig. 39 shows the results of TGA. A weight loss of about 15.6% was observed between about 65 and 200 degrees C. Fig. 40 shows the results of PXRD. Peaks, in 2-theta angles, that can be used to characterize the solvate include any 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 of the following: 3.77, 7.57, 8.21, 11.33, 14.23, 16.15, 18.69, 20.63, 22.69 and 24.77 degrees or any one or any combination of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more peaks of Fig. 40. The other peaks of the graphs may also be used alone or in any combination to characterize the solvate.

Example 19

Propylene Glycol Solvate of Celecoxib Potassium Salt

A propylene glycol solvate of the potassium salt of celecoxib was prepared. To a solution of celecoxib (253 mg, 0.664 mmol) in Et_2O (6 mL) was added propylene glycol (0.075 mL, 1.02 mmol). To the clear solution was added KOtBu in THF (1 M, 0.66 mL, 0.66 mmol). Crystals immediately began to form. After 5 minutes, the solid had completely crystallized. The solid was collected by filtration and was washed with Et_2O (10 mL). The white solid was then air-dried and collected. This solid was a 1:1 solvate. The solid was characterized by TGA and PXRD. The results are depicted in Fig. 41 and 42.

Fig. 41 shows the results of TGA. A weight loss of about 14.94% was observed between about 65 and about 250 degrees C. Fig. 42 shows the results of PXRD. Peaks, in 2-theta angles, that can be used to characterize te solvate include any 1, 2, 3, 4, 5, 6, 7, 8 , 9, or 10 of the following: 3.75, 7.47, 11.33, 14.93, 15.65, 18.31, 20.47, 21.71, 22.51, and 24.97 degrees or any one or any combination of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more peaks of Fig. 42.

Example 20

Propylene Glycol Solvate of Celecoxib Lithium Salt

A propylene glycol solvate of the lithium salt of celecoxib was prepared. To a solution of celecoxib (264 mg, 0.693 mmol) in Et_2O (8 mL) was added propylene glycol (0.075 mL, 1.02 mmol). To the clear solution was added tBu-Li in pentane (1.7 M, 0.40 mL, 0.68 mmol). A brown solid formed immediately but dissolved within one minute

yielding a white solid. The white solid crystallized completely after 10 minutes. The solid was collected by filtration and was washed with Et_2O (10 mL). The white solid was then air-dried and collected. The solid was a 1:1 solvate. The solid was characterized by TGA and PXRD.

The results of TGA are depicted in Fig. 43 and show a weight loss of about 16.3% between 50 degrees C and 210 degrees C. The results of PXRD are shown in Fig. 51. Characteristic peaks of 2-theta angles that can be used to characterize the salt include any one, or combination of any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 of 3.79, 7.51, 8.19, 9.83, 11.41, 15.93, 18.29, 19.19, 19.87, 20.63, 22.01, or 25.09 degrees or any one or any combination of peaks of Fig. 51.

Example 21

Propylene Glycol Solvate of Celecoxib Sodium Trihydrate

Preparation:

a.) Celecoxib Na propylene glycol trihydrate was formed by allowing the celecoxib sodium salt propylene glycol solvate to sit at 60 % RH and 20 degrees C for 3 days. (Note: Formation of the trihydrate at 75 % and 40 degrees C as well). The trihydrate begins to form somewhere between 31 and 40 % RH at room temperature.

The results of TGA and PXRD are shown in Fig. 44 and 45. Fig. 44 shows the results of TGA where an about 9.64% weight loss was observed between room temperature and 60 degrees C and an about 13.6% weight loss was observed between about 60 degrees C and 175 degrees C.

The PXRD pattern has characteristic peaks at 2-theta angles shown in Fig. 45. Any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more peaks can be used to characterize the trihydrate, including for example, peaks at 3.47, 6.97, 10.37, 13.97, 16.41, 19.45, 21.29, 22.69, 23.87, and 25.75 degrees.

b.) The trihydrate can also be formed by crystallization of celecoxib Na propylene glycol solvate in the presence of H_2O. To a solution of celecoxib (136.2 mg; 0.357 mmol) in Et_2O (6.0 mL), H_2O (0.025 mL; 1.39 mmol), and propylene glycol (0.030 mL; 0.408 mmol) was added NaOEt in EtOH (21 wt. %; 0.135 mL; 0.362 mmol). A solid formed within one minute and was isolated via filtration. The solid was then washed with

additional Et_2O (2.0 mL) and allowed to air dry. This procedure gives essentially the same PXRD pattern but there is a slight excess of H_2O, which is probably surface water.

The results of TGA and PXRD are shown in Fig. 46 and 47. Fig. 46 shows the results of TGA where an about 10.92% weight loss was observed between room temperature and 50 degrees C and an about 12.95% weight loss was observed between about 50 degrees C and 195 degrees C.

The PXRD pattern has characteristic peaks at 2-theta angles shown in Fig. 47. Any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or more peaks can be used to characterize the trihydrate, including for example, peaks at 3.43, 6.95, 10.25, 13.95, 16.39, 17.39, 17.75, 18.21, 19.43, 21.21, 22.61, and 25.71 degrees.

Example 22

Isopropyl Alcohol Solvate of Celecoxib Sodium Salt

To a solution of celecoxib (204.2 mg; 0.5354 mmol) in Et_2O (6.0 mL) was added iPrOH (0.070 mL). To the colorless solution was added a solution of NaOMe (0.5 M; 2.52 mL; 6.75 mmol) in MeOH followed by hexanes (3.0 mL). The volatiles were reduced under flowing N_2 gas. A white solid formed and was collected via filtration. After drying, the solid was found to be an isopropanol solvate (1.5:1 isopropanol:celecoxib) via TGA.

The results of DSC, TGA and PXRD analysis are shown in Figs. 48-50. Fig. 48 shows the results of DSC analysis where a peak endotherm was observed at 67.69 degrees C. The results of TGA, as shown in Fig. 49, revealed a weight loss of about 18.23% from about room temperature to about 120 degrees C.

The PXRD pattern has characteristic peaks at 2-theta angles shown in Fig. 50. Any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or more peaks can be used to characterize the solvate, including for example, peaks at 3.43, 7.03, 10.13, 11.75, 14.11, 16.61, 17.61, 18.49, 19.51, 20.97, 22.33, 22.81, and 25.93 degrees.

Example 23

1:1 Celecoxib:Nicotinamide Co-crystals

Celecoxib (100 mg, 0.26 mmol) and nicotinamide (32.0 mg, 0.26 mmol) were each dissolved in acetone (2 mL). The two solutions were mixed and the resulting mixture was

allowed to evaporate slowly overnight. The precipitated solid was collected and characterized. Detailed characterization of the co-crystal was performed using DSC, TGA & PXRD. The results of DSC showed two phase transitions at 117.2 and 118.8 degrees C and a sharp endotherm at 129.7 degrees C. The results of TGA showed decomposition beginning at ~150 degrees C. The results of PXRD is shown in Fig. 52. Characteristic peaks that can be used to characterize the co-crystal include any one, or any combination of any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 the peaks at 3.77, 7.56, 9.63, 14.76, 16.01, 17.78, 18.68, 19.31, 20.435, 21.19, 22.10, 23.80, 24.70, 25.295, and 26.73 degrees, or any one or any combination of any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more peaks of Fig. 52.

Example 24

Hydrates of Celecoxib Sodium Salt and Celecoxib Sodium Propylene Glycol Solvate

As discussed above, the celecoxib sodium is a variable hydrate. To analyze the affect of hydration on crystal structure, the celecoxib sodium salt and celecoxib sodium salt propylene glycol solvate were analyzed by PXRD under 17 %, 31 %, 59 % and 74 % constant relative humidity at room temperature. The following table lists PXRD 2-theta angle (degrees) peaks at the different relative humidities.

Table 4

Celecoxib Sodium				Celecoxib Sodium Propylene Glycol			
17%	**31%**	**59%**	**74%**	**17%**	**31%**	**59%**	**74%**
3.51	3.51	3.49	3.59	3.79	3.82	3.47	3.47
3.99	3.95	3.95	4.61	7.65	7.61	6.97	6.97
8.87	8.89	4.61	5.35	8.75	8.69	10.29	10.29
9.51	10.69	5.35	8.91	11.45	11.47	11.91	11.85
10.75	11.59	7.83	9.51	12.19	12.19	13.03	12.97
11.59	11.97	8.91	10.71	16.47	15.29	13.95	13.97
13.39	13.31	9.19	11.29	18.43	15.88	16.41	16.39
18.47	14.47	11.65	12.99	19.21	16.43	17.39	17.39
19.09	18.49	12.21	13.85	20.91	17.19	17.79	17.79
20.17	19.05	12.97	14.43	22.05	18.45	18.23	18.23
21.55	20.13	13.87	14.83	22.97	19.17	19.45	19.45

21.91	20.43	14.79	16.07		20.84	20.59	20.63
31.67	21.53	16.05	16.75		22.09	21.27	21.27
	21.85	17.47	17.13		22.95	22.67	22.63
	22.75	18.43	17.97		23.99	23.91	23.91
	31.69	18.89	18.39		25.47	24.37	24.35
		19.57	18.71		31.05	25.71	25.71
		20.13	19.63			29.09	27.83
		20.43	19.89			31.33	29.11
		21.57	20.43			31.83	31.31
		22.41	21.55			32.79	31.87
		24.53	22.39			33.55	32.83
		25.37	23.43				33.59
		25.75	24.55				
		27.23	25.35				
		27.69	25.71				
		29.49	27.13				
		30.11	27.69				
		31.70	28.19				
		35.23	29.49				
		37.95	29.99				
			32.29				
			37.87				

The composition can be characterized by any one or combination of any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more peaks listed in Table 4 or any one or combination of any 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or more peaks of any one of Figs. 53-60. Fig. 53-56 are PXRD diffractograms of celecoxib sodium hydrates at 17 %, 31 %, 59 %, and 74 % RH, respectively. Fig. 57-60 are PXRD diffractograms of celecoxib sodium propylene glycol hydrates at 17 %, 31 %, 59 %, and 74 % RH, respectively.

Example 25

Various Hydrates of Celecoxib Sodium Salt

Multiple celecoxib sodium salt samples, all form M1, varying in hydration (believed to range from about 0.5-4 equivalents of H_20 per equivalent of celecoxib) were assayed by PXRD. The PXRD patterns were then grouped based on shared peaks. Several groups were identified with four shown in Fig. 61. Group D is consistent with a mixture of

amorphous and crystalline celecoxib sodium. Table 5 lists PXRD peaks characteristic in common to groups A, B, and C and peaks that are specific to each group.

Table 5

Peaks common to all Variants of form M1	Peaks for form M1_A	Peaks for form M1_B	Peaks for form M1_C
3.7 ± 0.3°	9.5 ± 0.2°	9.5 ± 0.2°	12.1 ± 0.2°
8.9 ± 0.2°	11.3 ± 0.2°	11.4 ± 0.2°	14.7 ± 0.2°
10.7 ± 0.2°	17.2 ± 0.2°	13.3 ± 0.2°	
20 ± 0.2°		14.4 ± 0.2°	
21.8 ± 0.3°			

Example 26

Isolation of Valdecoxib from Bextra™ Tablets and Crystallization of Valdecoxib Isopropanol Solvate

20 mg Bextra™ tablets were crushed to a fine powder and tetrahydrofuran (THF) was added (75 mL). The suspension was allowed to stir at 50 degrees C for 30 minutes. At this point the mixture was filtered and the filtrate was collected. The volatiles were removed in vacuo yielding a colorless oil, which slowly forms a crystalline solid. The solid was then recrystallized from isopropanol (80 mL) to give the white crystalline solvate.

Valdecoxib isopropanol solvate is characterized by a very broad endothermic transition observed by differential scanning calorimetry (DSC) between 60 and 150 degrees C, and sharp endothermic transitions at 160 and 170 degrees C (Fig. 62).

TGA showed the valdecoxib isopropanol solvate loses <1 % of its weight between room temperature and 50°C and 14-17 % of its weight between 50 and 150 degrees C (Fig. 63).

PXRD analysis showed peaks occurring at, for example, 2 theta angles of 10.95, 11.89, 14.07, 17.15, 19.45, and 21.29 degrees (Fig. 64).

When analyzed by Raman spectroscopy, the valdecoxib isopropanol solvate exhibited Raman shifts at about 1634.5, 1601.5, 1161, 1032.5, and 1006 cm^{-1} (Fig. 65).

^1H NMR spectroscopy (Fig. 66) and TGA verified the presence of approximately one stoichiometric equivalent of isopropanol. (NMR acquisitions were performed on a Varian 300 MHz spectrometer in (dimethyl sulfoxide)-d^6.)

Example 27

Valdecoxib Sodium Salt

The isopropanol solvate of valdecoxib (Example 26, 113.0 mg, 0.3189 mmol) was suspended in an aqueous solution of NaOH (3 mL, 1 M). The suspension was gently heated at 60 degrees C for 30 minutes to dissolve most of the solid, although some remained in suspension. The mixture was allowed to cool to room temperature, which yielded no precipitation. Further cooling to 4 degrees C also gave no precipitation of the product. The solvent (H_2O) was evaporated resulting in a white solid. The solid was washed with H_2O (5 mL) and filtered to yield another white solid. The solid was allowed to air dry resulting in a white crystalline powder.

DSC analysis of valdecoxib sodium salt showed a sharp endothermic transition at about 154.3 degrees C (Fig. 67).

TGA showed the valdecoxib sodium salt loses about 10 percent to about 15 percent of its weight when the temperature is raised from 25 degrees C to 225 degrees C (Fig. 68).

PXRD analysis showed peaks occurring at 2 theta angles of about 3.73, 13.11, 15.43, 16.57 and 20.85 degrees (Fig. 69).

Raman spectroscopy showed Raman shifts occurring at about 1629, 1604, 1445, 1156, and 1001 cm^{-1} (Fig. 70).

^1H NMR spectroscopy was used to further characterize the valdecoxib sodium salt (Fig. 71). (NMR acquisitions were performed on a Varian 300 MHz spectrometer in (dimethyl sulfoxide)-d^6.)